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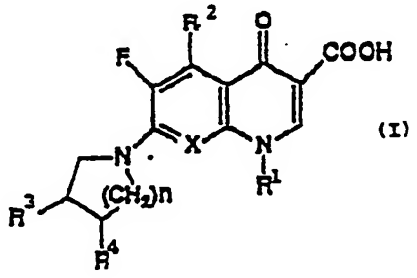
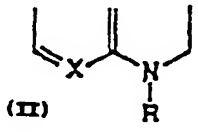
(54) Title: 7-SUBSTITUTED-6-FLUORO-1,4-DIHYDRO-4-OXO-QUINOLINE-3-CARBOXYLIC ACID COMPOUNDS USEFUL AS ANTIBACTERIAL AGENTS



(I)



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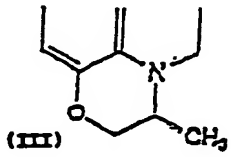

(III)

(57) Abstract

7-Substituted-6-fluor-1,4-dihydro-4-oxo-quinoline-, naphthyridine- and benzoxazine carboxylic acids of formula (I), wherein R^1 is a cycloalkyl group or a phenyl group which may be substituted by one or two halogen atoms; R^2 is hydrogen, a halogen atom, an alkyl group, a hydroxy group or an amino group; R^3 is hydrogen, hydroxy or amino; R^4 is a 1,2,3-triazol-1-yl group, a 1,2,4-triazol-1-yl group, a 1,2,3,4-tetrazol-1-yl or a 1,2,3,4-tetrazol-2-yl group, each of which may have 1 to 2 substituents selected from the group consisting of alkyl, COOH, CH_2NH_2, amino and phenyl groups; and x is N, CH, C-F or C-OCH_3; n is 0, 1 or 2; or (II) may be (III), are described, as well as a process for their preparation and their use as antibacterial agents

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+ DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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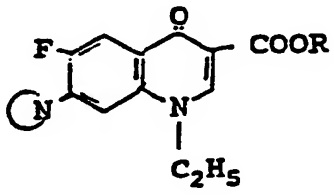
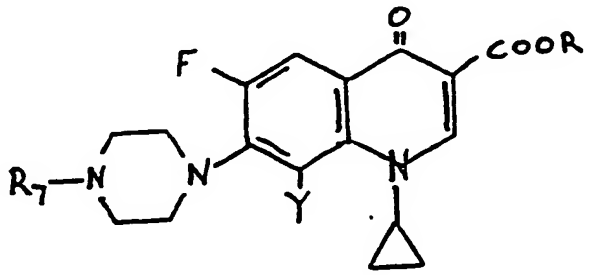
7-Substituted-6-Fluoro-1,4-Dihydro-4-Oxo-Quinoline-3-Carboxylic Acid Compounds Useful as Antibacterial Agents

Background of the Invention

Many clinically important antibacterial agents, collectively known as fluoroquinolones, have been discovered. Quinolones which possess a substituted 1,4-dihydro-4-oxo-quinoline-3-carboxylic acid moiety and which have the general structural formula given below are described in J. Med. Chem. 23, 358 (1980).



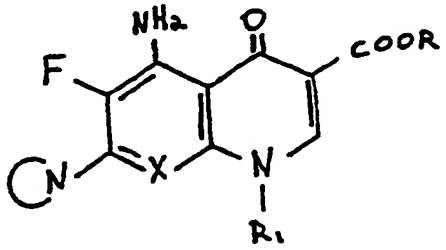
wherein N) may be piperazinyl or the like. Belgian Patent 899399 discloses 1-cyclopropyl-7-piperazinyldihydroquinoline carboxylic acid compounds of the formula



wherein R_7 is H or CH_3 and Y is Cl, F or CH_3.

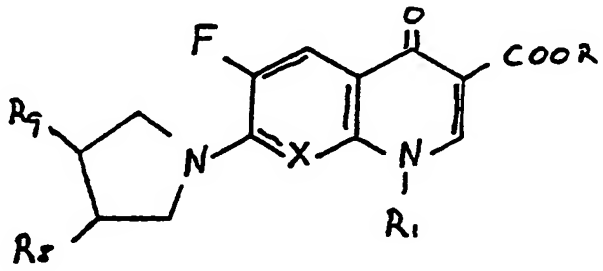
Japanese Patent No. 174367/1983, South African Patent No.

8502369, European Patent Nos. 172651 and 221463, 119087, U.S. Patent No. 4556658, 1985 and J. Med. Chem. 1990, 33 (1645-1656), disclose compounds represented by the following general formula having an amino group at position 5.



wherein R_1 is ethyl, cyclopropyl; X is CH, CF, C-CH_3; and N⌀ is piperazinyl or the like.

The 7-(3-aminopyrrolidinyl)quinolones which are represented by general formula given below:



wherein X is N, CH or CF; R_1 is ethyl, cyclopropyl, 2,4-difluorophenyl or 4-fluorophenyl; R_8 is NH_2, CH_2NH_2, pyrrole, imidazole or pyrrolidine group and R_9 is -OCH_3, CH_3, C_6H_5 or =CH_2 are disclosed in J. Med. Chem. 1988, 31 (1598-1611); J. Med. Chem. 1990, 33 (849-854); EP 347851, EP 362759, Abstracts of the 30th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, October 21-24, 1990, Abstract No. 395.

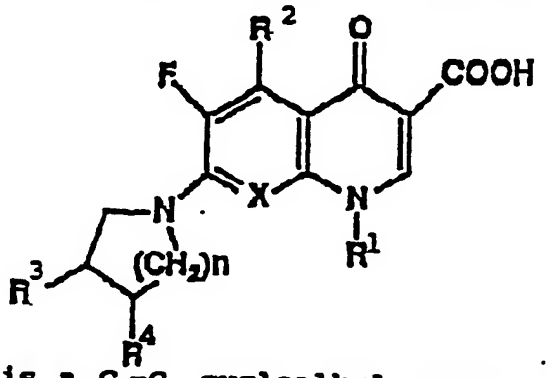
Some of the above disclosed compounds are clinically useful. However, there exists a continuing need to develop new antibacterial agents because the effectiveness of existing antibacterial agents diminishes as strains of pathogens develop resistance. In addition certain

antibiotics exhibit unsuitable pharmaceutical properties and exert serious adverse side effects in humans.

Summary of the Invention

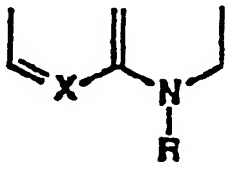
The present invention is based on the discovery that certain 7-substituted-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid compounds exhibit excellent activity against sensitive and resistant Gram-positive and moderate activity against Gram-negative bacteria.

In accordance with the present invention there is provided a 7-substituted-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid compound of the formula:

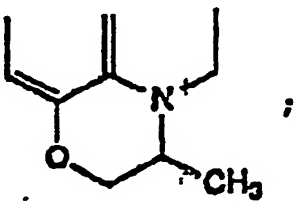


I

wherein R^1 is a C_3-C_6 cycloalkyl group or a phenyl group which may be substituted by one or two halogen atoms; R^2 is hydrogen, a halogen atom, a C_1-C_4 alkyl group, a hydroxy group or an amino group; R^3 is hydrogen, hydroxy or amino; R^4 is a 1,2,3,4-triazol-1-yl group, a 1,2,4-triazol-1-yl group, a 1,2,3,4-tetrazol-1-yl group or a 1,2,3,4-tetrazol-2-yl group, each of which may have 1 to 2 substituents selected from the group consisting of C_1-C_4 alkyl, -COOH, $-CH_2NH_2$, amino and phenyl group; and X is N, CH, C-F or $C-OCH_3$; n is 0, 1 or 2; or



may form the group



;

Preferably the C_1-C_4 alkyl group is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-

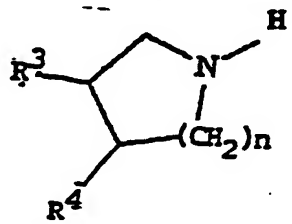
butyl; the C_3-C_6 cycloalkyl group is selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl and the optionally substituted phenyl is selected from phenyl, 4-fluorophenyl or 2,4-difluorophenyl. The groups which may be substituted, as discussed above, may be substituted with chlorine, bromine, fluorine or a methoxy group.
or a pharmaceutically acceptable salt thereof.

The compounds of the invention include those wherein the azetidine, pyrrolidine or piperidine moiety at the 7-position has an asymmetric carbon atom or atoms and can in optically active forms. Hence, this invention includes the R isomer, the S isomer and mixtures thereof. Some of the compounds of this invention have two asymmetric carbon atoms on the azetidine, pyrrolidine or piperidine moiety and therefore exist as stereoisomers having different configurations (i.e., cis-and trans-configurations). Such stereoisomers and their mixtures are also included within the compounds of this invention.

The compounds of this invention exhibit excellent antimicrobial activity against both sensitive and resistant Gram-positive bacteria. Compounds of formula I may be utilized as antibacterial active compounds in medicaments formulated with pharmaceutically acceptable carriers.

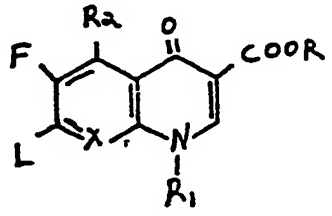
Description of the Preferred Embodiments

In general, the 7-substituted-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid compounds of formula I are prepared as follows:
Compounds having the general formula II are reacted with compounds having the general formula III under the conditions described hereinafter.



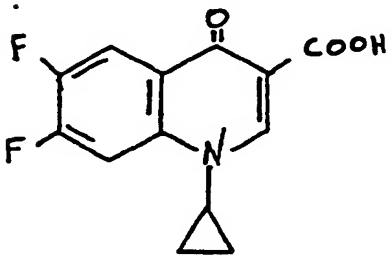
III

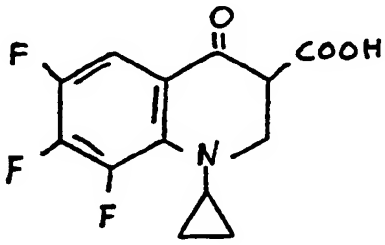
+



II

L is a suitable leaving group and may be chlorine, bromine, fluorine, SO_2R_7, wherein R_7 is a C_1-C_4 alkyl group or an unsubstituted or substituted phenyl group. The starting compounds having the formula II can be prepared from known starting materials using standard procedures or variations thereof within the skill of the art. Various starting compounds of formula II are known and are shown below in association with a reference citation:

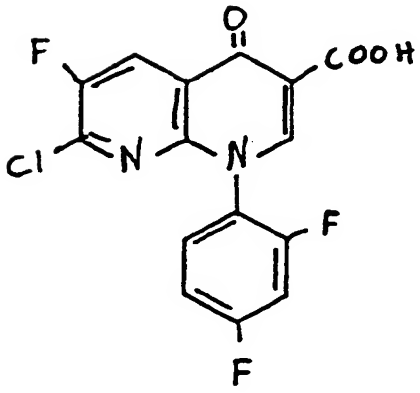


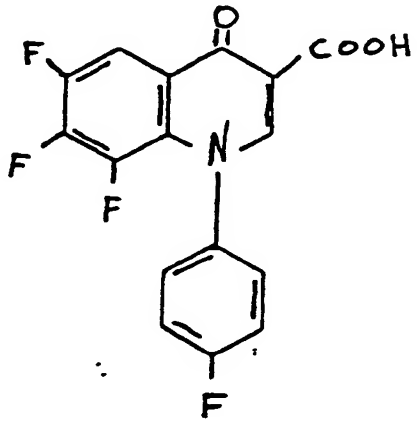


J. Med. Chem. 31, 903 (1988)

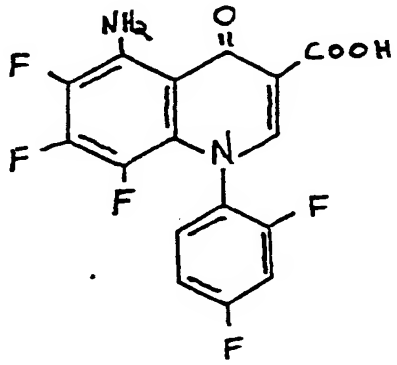
U.S. Patent 4,665,079

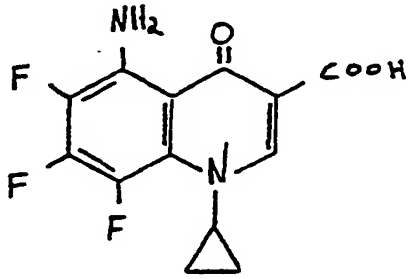
J. Med. Chem. 31, 99 (1988)





J.Med.Chem. 29, 2363 (1986) J.Med.Chem. 30, 504 (1987)

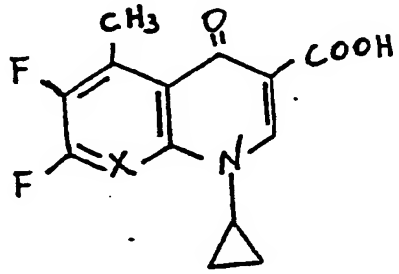




J. Med. Chem. 33, 1645 (1990)

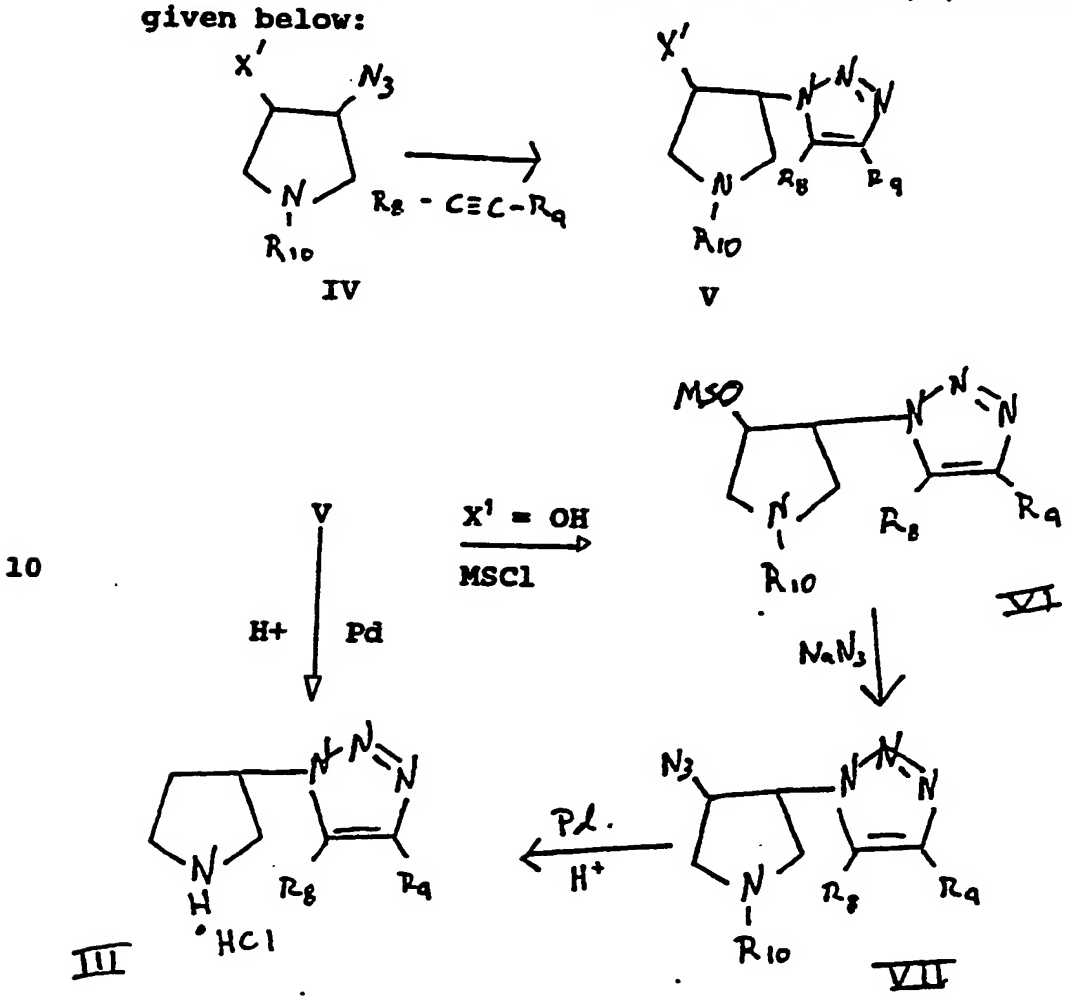
J. Med. Chem. 33, 1645 (1990) EP 0221 463

EP 0221 463



wherein X is nitrogen, or C-F or CH or C-CH_3 or C-CF_3 or C-OCH_3.

A schematic route for the preparation of compounds of formula III wherein the azole ring is a 1,2,3-triazole is given below:



wherein X^1 is hydrogen or hydroxy,

R_3 is hydrogen or hydroxy or amino group,

R_8 and R_9 are hydrogen C_1-C_4 alkyl, COOH, CH_2NH_2, amino or phenyl,

R_{10} is benzyl or t-BOC protective group.

The reaction of compound IV and a substituted

acetylene as shown is carried out in a suitable solvent such as acetone, methanol, ethanol, benzene, toluene or xylene, either in a high pressure vessel or at normal pressure. The reaction is usually carried out at temperature from room temperature to 150°C, preferably from 60° C to 140° C, for 2 to 96 hours. Substituted acetylenes are usually used in an amount of at least 1 mole, preferably 1 to 15 moles, for every one mole of compound IV.

Deprotection of the N-protective group of compound V is carried out either by hydrogenation in presence of an acid such as hydrochloric acid, acetic acid etc. or by hydrolysis with mineral acid such as HCl, HNO_3, H_2SO_4, CF_3COOH or CH_3COOH in a solvent such as methanol, ethanol or propanol. The deprotection reaction is usually carried out at a temperature from 0° C to 100° C, usually at 0° C to 40° C, for 10 minutes to 48 hours. The hydrogenation reaction is usually carried out in presence of metal catalyst such as Pd, Pt or Rh under normal pressure to high pressure.

The reaction of compound V and methane sulfonyl chloride (MSCl) is carried in a suitable solvent, for example, dichloromethane, chloroform, carbon tetrachloride, benzene, toluene, DMF or DMSO in the presence of a base such as triethylamine, $NaHCO_3$, K_2CO_3, $CsCO_3$, sodium alkoxide ($NaOCH_3$ or $NaOC_2H_5$), potassium tert-butoxide or pyridine. The reaction temperature is in the range from 0° C to 100° C, preferably 0° C to 35° C, and reaction times vary from 1 hour to 48 hours. The methanesulfonyl chloride is usually used in an amount of at least 1 mole preferably 1 to 5 moles per mole of compound V.

The reaction of compound VI and a metal azide such as NaN_3 in the presence of phase transfer catalyst such as NH_4Cl, $(NH_4)_2CO_3$, $(Bu)_4NBr$ is carried out in a polar solvent such as DMF or DMSO, etc. or in a mixture of solvents such as DMF-H_2O, DMSO-H_2O in a ratio of 4:1. The reaction temperature ranges from room temperature to 180° C,

preferably from 40° to 100° C. The reaction time ranges from 1 hour to 48 hours, and a molar ratio of from 1 to 5 moles of metal azide per mole of compound VI is preferred. The phase transfer catalysts are used in same ratio as the metal azide ratio.

The reaction condition for conversion of compound VII to compound III is the same as described for conversion of compound V to compound III.

Compounds of the formula III wherein the azole ring is a 1,2,4-triazole can be prepared by the reaction of potassium-1,2,4-triazolide with N-benzhydryl-3-mesyloxyazetidine or N-benzyl-3-mesyloxypyrrolidine. The N-blocking groups are then removed are in the usual manner by catalytic hydrogenation with palladium on charcoal, as illustrated in Examples U, V, W and X.

Compounds of the formula III wherein the azole ring is a 1,2,3,4-tetrazole moiety are prepared in an analogous manner as illustrated in Examples JJ, KK and LL.

Compounds of the formula III wherein n=o (azetidines) or n=2 (piperidines) are prepared in analogous manner to those wherein n-1 (pyrrolidines).

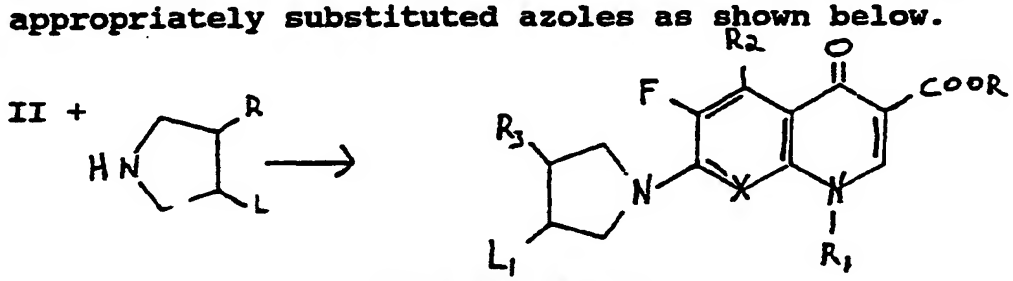
The starting compounds II and III are reacted together in the presence of solvents at elevated or reduced temperatures for a sufficient time to allow the reaction to proceed to completion. Reaction conditions will depend upon the nature of the leaving group L of the compounds of formula II and the degree of the reactivity of compound III.

The reaction is preferably carried out in the presence of a proton acceptor such as pyridine, diazabicycloundecane (DBU), N-methyl pyrrolidine-2-one or picoline.

The solvents of choice for this reaction are nonreactive solvents such as acetonitrile, tetrahydrofuran (THF), ethanol, methanol, chloroform, methylene chloride, pyridine, picoline, N-methylpyrrolidine-2-one, water, dimethyl sulfoxide, dimethylformamide or the like. Mixtures of these solvents may also be utilized.

Reaction temperatures will generally range from between about 50°C to 150°C. The preferred molar ratio of compounds II and III are 1:2.5 to 5.0. The reaction times generally range from 4 to 50 hours depending on the reactants.

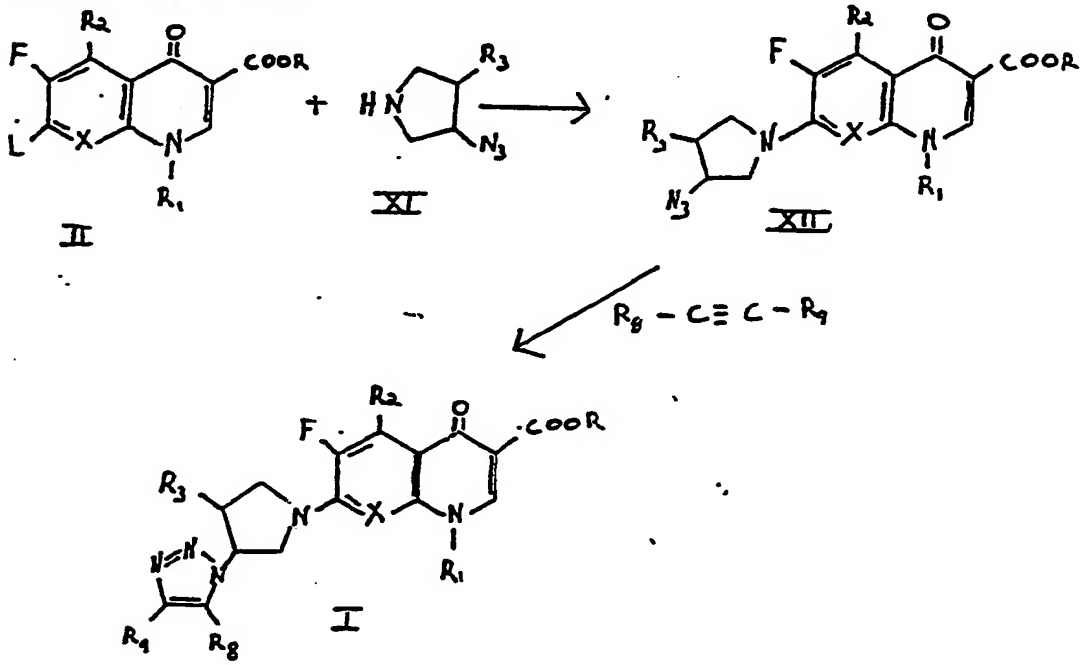
Another method for preparing compounds of formula I is by reacting a compound of the general formula II with a compound of formula VIII to form a compound of formula IX followed by substitution of leaving group L_1 in IX with the appropriately substituted azoles as shown below.



IX

R, R_1, R_2, R_3, R_4, X and L are the same as defined above. L_1 is the suitable leaving group selected from chlorine, bromine, fluorine or SO_2CH_3 or $SO_2C_6H_4$ CH_3(p).

An alternate process can also be used for preparing the compound of formula I by reacting the compound of formula II with compound of formula XI followed by reaction with substituted acetylenes as shown in the following scheme:



II XI XII I

R, R_1, R_2, R_3, R_4, R_5, R_8, R_9, X and L are same as defined above. The reaction time, temperature, molar ratio and solvent for the reaction of the compound of formula II with the compound of formula VIII or reaction of compound of formula II with compound of formula XI are the same as defined for the reaction of compound II with compound III, as described above.

The reaction temperature, time, molar ratio and solvent used for the reaction of compound IX with triazoles are the same as described above for the reaction of compound VI with metal azides (NaN_3) or $(C_4H_9)_4NN_3$. The reaction temperature, times, molar ratio and solvent used for the reaction of compound XII with substituted acetylenes are the same as described for the conversion of compound IV to compound V.

The pyrido-benzoxazine compounds of the invention are prepared as illustrated in Examples 41, 42 and 43 using the procedure described by Mitscher et al, J. Med. Chem. 30, 2283-2286 (1987) to prepare the pyrido-benzoxazine intermediate compounds of formula II.

The compounds of the invention are capable of forming both pharmaceutically acceptable acid addition and/or base salts. Base salts are formed with alkali and alkaline earth metals such as sodium, potassium, magnesium, calcium, and the like, and heavy metal salts such as silver, zinc, cobalt, and cerium, and with organic amines such as choline and lysine, either directly or in combination with a physiologically acceptable carrier.

Pharmaceutically acceptable acid addition salts are formed with organic and inorganic acids such as hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, gluconic, fumaric,

succinic, ascorbic, maleic, methanesulfonic, p-toluenesulfonic acid and the like. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid or amine to produce, for example, the mono or di salt in a conventional manner.

The compounds of the invention can exist in unsolvated as well as solvated forms including hydrated forms and the like. In general, the solvated forms, including hydrated forms, are equivalent to the unsolvated forms for purpose of the invention.

The compounds of formula I are useful as antibacterial agents. They were found to be very potent in vitro against various sensitive and quinoline resistant Gram positive microbes such as E. faecium, S. aureus Cog.-ve, S. epidermidis, S. saprophyticus, and S. pyogenes. Further studies on some of the compounds of this invention revealed that their in vitro MIC values against Gram-positive and Gram-negative organisms are negligibly affected by inoculum size, cations (Mg^{++}, Ca^{++}), and serum.

Human patients suffering from bacterial infections can be treated by administering to the patient a pharmaceutically effective amount of one or more of the present compounds optionally, but preferably, in the presence of a pharmaceutically acceptable carrier or diluent. There may also be included a pharmaceutically compatible binding agent, and/or adjuvant materials. The active materials can also be mixed with other active materials which do not impair the desired action and/or supplement the desired action. The above materials according to the present invention can be administered by any route, for example, orally, parenterally, intravenously, intradermally, subcutaneously or topically in solid or liquid form.

The solid form preparation includes powders, tablet, dispensable granules, capsules, cachets, suppositories and ointments. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or

tablet disintegrating agents, including magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, gum tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting wax, cocoa butter and the like.

Liquid form preparations include solutions, suspensions and emulsions. The liquid preparation for parenteral injection may be water or water-propylene glycol solution or water-polyethylene glycol solution or the like, so long as it is acceptable to biological systems (isotonicity, pH etc.). Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorant, flavors, stabilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e. natural or synthetic gum, resins, methyl cellulose, sodium carboxymethyl cellulose and other well known suspending agents.

The quantities of active compound in a unit dose of a preparation may be varied depending on the particular application and the potency of the active ingredient. Determination of the proper dosage for a particular situation is within the skill of the art. The dosage of the pharmaceutical preparation is generally in the range of 0.2 to 100 mg of the compound of formula I and salts thereof per kilogram of body weight of the patient per day. Preferably this daily dose is administered 2 - 4 times per day in fractions of the daily dose.

Our invention is further illustrated by means of the following non-limiting examples:

Example 1

Ethyl 6,8-difluoro-1-(4-fluorophenyl)-7-[3-(1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylate

A solution of ethyl 1-(4-fluorophenyl)-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylate (180

mg, 0.5 mmol), 3-(1,2,3-triazol-1-yl)-pyrrolidine hydrochloride (259 mg, 1.4 mmol) and DBU (384 mg, 2.5 mmol) in acetonitrile (20 ml) was heated at 75° for 3 h. Cooled to r.t. and stirred for another 15 h. The separated solid was filtered, successively washed with acetonitrile and ether. The white crystalline solid thus obtained was dried in vac-oven at 40°C. Yield: 135 mg. 56.7%. ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, 3H), 2.50 (m, 2H), 3.70 (m, 1H), 3.85 (m, 2H), 4.10 (m, 1H), 4.35 (q, 2H), 5.25 (m, 1H), 7.20 (m, 2H), 7.40 (m, 2H), 7.63 (d, 1H), 7.72 (d, 1H), 7.90 (dd, 1H), 8.25 (S, 1H).

Example 2

6,8-Difluoro-1-(4-fluorophenyl)-7-[3-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A suspension of ethyl 6,8-difluoro-1-(4-fluorophenyl-7-[3-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylate (180 mg, 0.37 mmol) in 20 ml NaOH solution (containing 15 mg NaOH) and THF (20 ml) was heated at 90° C for 3.5 h. The THF was evaporated and the separated solid redissolved in water layer by heating and acidified to pH 6.0. The precipitate was filtered, washed with water and dried in vac-oven at 40° C to obtain the title compound as a light yellow solid. Yield: 89 mg, 52.66%; m.p. 303° C. ^{1}H NMR (TFA) δ: 2.82 (m, 2H), 4.14-4.64 (m, 4H), 5.74 (m, 1H), 7.37 (m, 2H), 7.60 (m, 2H), 8.20 (dd, 1H), 8.54 (d, 1H), 8.65 (d, 1H), 9.03 (S, 1H).

Example 3

Ethyl 1-(2,4-difluorophenyl)-6-fluoro-7-[3-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate

A mixture of ethyl 1-(2,4-difluorophenyl)-7-chloro-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (91 mg, 0.5 mmol), 3-(1,2,3-triazol-1-yl)-pyrrolidine hydrochloride (259 mg, 1.5 mmol), and DBU (380 mg, 2.5 mmol) in CH_3CN (20 ml) was heated under reflux for 2 h,

cooled to r.t. and stirred further for 18 h, diluted with water. Unreacted starting materials were removed by extraction with chloroform. The water layer was concentrated to give a yellow oil. Yield: 150 mg, (62%). ^{1}H NMR ($CDCl_3$) δ: 1.3 (t, 3H), 2.5 (m, 2H), 3.9 (m, 4H), 4.4 (q, 2H), 5.3 (m, 1H), 7.3 (m, 4H), 7.8 (d, 1H), 8.0 (d, 1H), 8.4 (s, 1H).

Example 4

Ethyl 1-cyclopropyl-6-fluoro-7-[3(S)-(1,2,3-triazol-1-yl)pyrrolidin-1-yl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate

Ethyl-7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (250 mg, 0.8 mmole) was reacted with 350 mg (2 mmole) of 3(S)-(1,2,3-triazol-1-yl)pyrrolidine hydrochloride in 8 ml of pyridine in the presence of 305 mg (2 mmol) of DBU at 80-90 C for 6 hr. The reaction was then stirred at room temperature for 4 days. The solvent was then evaporated under reduced pressure and to the residue, water was added and extracted with chloroform. The organic layer was dried and evaporated to dryness. The residue was then chromatographed over aluminum (neutral, activity III) using chloroform as solvent to yield 80 mg (24%) of the desired product. ^{1}H NMR ($CDCl_3$) : 8.48 (s, 1H), 8.05 (d, 1H), 7.76 (d, 1H), 7.7.1 (d, 1H), 5.46-5.32 (m, 1H), 4.46-4.26 (m, 4H), 4.15-4.0 (m, 2H), 3.56-3.42 (m, 1H), 2.71-2.57 (m, 2H), 1.4 (t, 3H), 1.26-0.95 (m, 4H).

Example 5

1-Cyclopropyl-6-fluoro-7-[3(S)-(1,2,3-triazol-1-yl)pyrrolidin-1-yl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

Ethyl 1-cyclopropyl-6-fluoro-7-[3(S)-(1,2,3-triazol-1-yl)pyrrolidin-1-yl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (80 mg, 0.19 mmol was heated in 16 ml of 6N HCl at 100-110° C for 18 hr. This was then concentrated to dryness and methanol-ether was added and the formed

solid was collected to yield 55 mg (73%) of the desired product after drying, m.p. 268-270° C. ^{1}H NMR (TFA) : 9.21 (s, 1H), 8.74 (s, 1H), 8.58 (s, 1H), 8.20 (d, 11.4 Hz, 1H), 6.14-5.84 (m, 1H), 4.94-4.3 (m, 4H), 4.18-3.95 (m, 1H), 3.18-2.8 (m, 2H), 1.68-1.18 (m, 4H).
Anal. calcd. for $C_{18}H_{17}FN_6O_3 \cdot 1/2H_2O$; C, 54.96; H, 4.61; N, 21.35. Found; C, 54.66; H, 4.51; N, 20.85.

Example 6

Ethyl 7-[cis-3-amino-4-(1,2,3-triazol-1-yl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate

Ethyl 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (243 mg, 0.78 mmole) and cis-3-amino-4-(1,2,3-triazol-1-yl)pyrrolidine (300 mg, 1.96 mmole) were reacted together in 8 ml of pyrridine at room temperature for 5 days. The solvent was then evaporated, water was added to the residue and was extracted with chloroform. The organic layer was then dried (Na_2SO_4) and evaporated to yield 0.23 g of the crude product which upon purification over neutral alumina (activity III) using 4% methanol/chloroform as solvent yielded 200 mg (60%) of the desired product. ^{1}H NMR ($CDCl_3$) : 8.5 (s, 1H), 8.12 (d, 1H), 7.82 (s, 1H), 7.76 (s, 1H), 5.3-5.15 (s, 1H), 4.55-4.00 (m, 6H), 3.85-3.62 (m, 1H), 3.58-3.4 (m, 1H), 1.43 (t, 3H), 1.32-0.94 (m, 4H).

Example 7

7-[cis-3-Amino-4-(1,2,3-triazol-1-yl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihdyro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride

Ethyl 7-[cis-3-amino-4-(1,2,3-triazol-1-yl)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (200 mg, 0.47 mmole) was heated with 8 ml of 6N hydrochloric acid at 110°C for 18 hr. The solution was then evaporated to dryness and the residue was crystallized from methanol-ether to yield 160

mg (85%) of the desired hydrochloride, m.p. 240° C (dec). ^{1}H NMR (TFA) : 9.27 (s, 1H), 9.01 (s, 1H), 8.66 (s, 1H), 8.3 (d, 11.6 Hz, 1H), 6.64-6.45 (m, 1H), 5.35-4.66 (m, 5H), 4.20-4.02 (m, 1H), 1.7-1.2 (m, 4H).Anal. calcd. for $C_{18}H_{19}ClFN_7O_3.1\frac{1}{2}H_2O$ C, 46.76; H, 4.80; N, 21.2; Cl, 7.67. Found; C, 46.85; H, 4.31; N, 20.62; Cl, 8.36.

Example 8

1-(2,4-Difluorophenyl)-6-fluoro-7-[3-(1,2,3-triazol-1-yl)pyrrolidin-1-yl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

A mixture of crude ethyl 1-(2,4-difluorophenyl)-6-fluoro-7-[3-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-1,8-napthyridine-3-carboxylate (150 mg, 0.31 mmol), THF (15 ml), NaOH (20 mg, 1.5 mmol) and water 15 ml was heated under reflux for 3 h, cooled and the THF evaporated. The aqueous solution was acidified and the precipitated yellow solid washed with water, dried in vac-oven at 50° C to obtain 80 mg (solid). This solid was washed with ether to get the pure of compound. Yield: 50 mg (35.7%) m.p.: 253° C (dec.). ^{1}H NMR (TFA) δ: 2.85 (m, 2H), 3.70-4.50 (m, 4H, 5.80 (m, 1H), 7.20 (m, 2H), 7.60 (m, 1H), 8.25 (s, 1H), 8.57 (S, 1H), 8.62 (S, 1H), 9.20 (S, 1H).

Example 9

1-Cyclopropyl-6-fluoro-7-(3-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (120 mg, 0.486 mmol), DBU (190 mg, 1.25 mmol), 3-(1,2,3-triazol-1-yl)pyrrolidine hydrochloride (216 mg, 1.25 mmol) in pyridine (8 ml) was heated at 80° C for 18 h. The reaction mixture was concentrated and treated with water. The separated solid was collected by filtration, washed with water and acetonitrile to give light brown solid. Yield: 71 mg (38%), m.p. 284° C (dec). ^{1}H NMR (TFA) δ: 1.5 (m, 4H),

3.0 (m, 2H), 4.0 (m, 4H), 4.65 (bs, 1H), 5.9 (bs, 1H), 7.5 (d, 1H), 8.20 (d, 1H), 8.6 (s, 1H), 8.7 ((s, 1H), 9.2 (s, 1H).

Example 10

1-Cyclopropyl-6,8-difluoro-7-[3-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (138.5 mg, 0.486 mmol), DBU (190 mg, 1.25 mmol), and 3-(1,2,3-triazol-1-yl)-pyrrolidine hydrochloride (216 mg, 1.25 mmol) in pyridine (8 ml) was heated for 20 h at 75-80° C and then pyridine removed under vacuum. The residue was diluted with acetonitrile. The precipitated solid was washed with acetonitrile, ether and dried at 40° C. Yield: 65 mg (33%) m.p. 244-246° C (dec.). ^{1}H NMR 25 (TFA) δ:1.5 (m, 4H), 2.8 (m, 2H), 4.5 (m, 4H), 4.75 (bs, 1H), 5.8 (bs, 1H), 8.15 (d, 1H), 8.6 (s, 1H), 8.7 (s, 1H), 9.25 (s, 1H).

Example 11

5-Amino-1-cyclopropyl-6,8-difluoro-7-[3-(1,2,3-triazol-1-yl)-pyrrilidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (190 mg, 0.64 mmol), 3-(1,2,3-triazol-1-yl)-pyrrolidine hydrochloride (290 mg, 1.67 mmol), and DBU (255 mg, 1.70 mmol) in pyridine (5 ml) was heated at 110° C for 20 h. The reaction mixture was then cooled and diluted with methanol. the separated solid was collected and washed successively with methanol, water and acetonitrile. The title compound was obtained upon drying in oven at 40° C. Yield: 168 mg (63%) m.p.: 273.5-275° C. ^{1}H NMR (TFA) δ: 1.40 (m, 4H), 2.90 (m, 1H), 4.40 (m, 4H), 4.75 (m, 1H), 5.70 (m, 1H), 8.55 (d, 1H), 8.68 (d, 1H), 9.15 (S, 1H).

Example 12

5-Amino-1-cyclopropyl-6,8-difluoro-7-[3S-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (200 mg, 0.67 mmol), 3S-(1,2,3-triazol-1-yl)pyrrolidine hydrochloride (293 mg, 1.68 mmole) and diazabicycloundecane (256 mg, 1.60 mmol) in pyridine (20 ml) was heated at 110° C for 20 hrs. The reaction mixture was cooled, diluted with methanol, the separated solid was filtered and washed with H_2O and CH_3CN, dried to give title product. Yield: 120 mg (43%), m.p. 277-78° C. ^1H NMR (TFA) δ: 1.31-1.58 (m, 4H), 2.90 (m, 2H), 4.15-4.54 (m, 4H), 4.75 (m, 1H), 5.86 (m, 1H), 8.55 (d, 1H), 8.69 (d, 1H), 9.15 (S, 1H).

Example 13

5-Amino-1-cyclopropyl-6,8-difluoro-7-[3R-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

Prepared by the same procedure as described in Example 12 by using 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid and 3R-(1,2,3-triazol-1-yl) pyrrolidine hydrochloride. Yield 41%, m.p. 279-280° C. ^1H NMR (TFA) δ: 1.31-1.49 (m, 4H), 2.92 (m, 2H), 4.2-5.1 (m, 4H), 4.73 (m, 1H), 5.82 (m, 1H), 8.56 (d, 1H), 8.68 (d, 1H), 9.10 (s, 1H).

Example 14

5-Amino-1-(2,4-difluorophenyl)-6,8-difluoro-7-[3-(1,2,3-triazol-1-yl)pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3 carboxylic acid

A mixture of 5-amino-1-(2,4-difluorophenyl)-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (200 mg, 0.54 mmol), 3-(1,2,3-triazol-1-yl)pyrrolidine hydrochloride (231 mg, 1.25 mmol) and diazabicycloundecane (200 mg, 1.31 mmol) in acetonitrile (25 ml) was refluxed for 45 hrs. The separated solid was filtered, washed with

acetonitrile and ether to give 150 mg (57%) of desired product, m.p. 307.5-309° C. ^{1}H NMR (TFA) δ: 2.81 (m, 2H), 4.06-4.53 (m, 4H), 5.73 (m, 1H), 7.15-7.23 (m, 2H), 7.59-7.66 (m, 1H), 8.52 (d, 1H), 8.62 (d, 1H), 8.82 (d, 1H).

Example 15

5-Amino-1-(2,4-difluorophenyl)-6,8-difluoro-7-[3S-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 5-amino-1-(2,4-difluorophenyl)-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (100 mg, 0.27 mmol), 3S-(1,2,3-triazol-1-yl)pyrrolidine hydrochloride (117 mg, 0.67 mmol) and diazabicycloundecane (102 mg, 0.67 mmol) in pyridine (10 ml) was heated at 110° C for 40 hrs. The reaction mixture was concentrated and the residue was triturated with water. The separated solid was filtered, washed with water, acetonitrile and dried under vacuum at 40° C. Yield: 88 mg (67%); m.p. 302-304° C. ^{1}H NMR (TFA) δ: 2.82 (m, 2H), 4.0-4.53 (m, 4H), 5.73 (m, 1H), 7.10-7.23 (m, 2H), 7.55-7.70 (m, 1H)8.52 (d, 1H), 8.62 (d, 1H), 8.82 (d, 1H).

Example 16

5-Amino-1-(2,4-difluorophenyl)-6,8-difluoro-7-[3R-(1,2,3-triazol-1-yl)-pyrrolidine-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

Prepared by following the procedure as described in Example 15 by using 5-amino-1- 2,4-difluorophenyl)-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid and 3R-(1,2,3-triazol-1-yl)pyrrolidine hydrochloride. Yield: 57%, m.p. 302.5-304° C. ^{1}H NMR (TFA) δ: 2.80-2.90 (m, 2H), 4.05-4.35 (m, 3H), 4.55 (m, 1H), 5.73 (m, 1H), 7.09-7.23 (m, 2H), 7.55-7.70 (m, 1H), 8.53 (d, 1H), 8.62 (d, 1H), 8.82 (d, 1H).

Example 17

7-[cis-3-Amino-4-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-

carboxylic acid

A mixture of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (44 mg, 0.156 mmol) and cis-3-amino-4-(1,2,3-triazol-1-yl)pyrrolidine (60 mg, 0.39 mmol) in pyridine (5 ml) was heated at 110° C for 2-3 hrs under N_2 and then stirred at room temperature for 20 hrs. The reaction mixture was concentrated and the residue was washed with water and acetonitrile. The solid was dried under vacuum at 40° C. Yield: 43 mg (66%), m.p. 245-47° C. ^1H NMR (TFA) δ: 1.3-1.8 (m, 4H), 4.4-5.25 (m, 6H), 6.40 (m, 1H), 8.15 (d, 1H), 8.62 (S, 1H), 8.90 (S, 1H), 9.40 (S, 1H).

Example 18

5-Amino-7-[cis-3-amino-4-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

Prepared by following the same procedure as described for Example 17 by using 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid and cis 3-amino-4-(1,2,3-triazol-1-yl) pyrrolidine. Yield: 65%, m.p. 275-277° C. ^1H NMR (TFA) δ: 1.33-1.50 (m, 4H), 4.32-5.12 (m, 6H), 6.34 (m, 1H), 8.64 (S, 1H), 8.89 (S, 1H), 9.16 (S, 1H).

Example 19

5-Amino-7-[cis-3-amino-4-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1-(2,4-difluorophenyl)-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

Prepared by following the same procedure as described for example 13 by using 5-amino-1-(2,4-difluorophenyl)-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid and cis 3-amino-4-(1,2,3-triazol-1-yl)-pyrrolidine. Yield: 66%, m.p. 279-281° C. ^1H NMR (TFA) δ: 4.48-4.82 (m, 4H), 5.02 (m, 1H), 6.26 (m, 1H), 7.17 (m, 2H), 7.62 (m, 1H), 8.6 (S, 1H), 8.82 (2d, 2H).

Example 20

5-Amino-7-[trans-3-hydroxy-4-(1,2,3-triazol-1-yl)-

pyrrolidin-1-yl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (63 mg, 0.21 mmol) trans-3-hydroxy-4-(1,2,3-triazol-1-yl)-pyrrolidine hydrochloride (100 mg, 0.52 mmol) and diazabicycloundecane (79 mg, 0.52 mmol) in pyridine was heated at 110° C for 20 hrs. The reaction mixture was concentrated and the residue was triturated with water. The separated solid was filtered, washed with water and acetonitrile and dried under vacuum at 40° C. Yield: 35 mg (40%); m.p. 261-165.5° C. ^{1}H NMR (TFA) δ: 1.33-1.51 (m, 4H), 4.24 (m, 2H), 4.60 (m, 2H), 4.92 (m, 1H), 5.20 (m, 1H), 5.79 (m, 1H), 8.59 (d, 1H), 8.78 (S, 1H), 9.15 (S, 1H).

Example 21

1-Cyclopropyl-6,8-difluoro-5-methyl-7-[3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

To the suspension of 50 mg (0.168 mmole) of 1-cyclopropyl-5-methyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine hydrochloride (79 mg, 0.421 mmole) in dry acetonitrile (5 ml) was added 64 mg (0.421 mmole) of DBU (diazbicycloundecane) and the solution was refluxed under nitrogen for 46 hr. The yellow solution was concentrated to dryness and the residue was then suspended in acetonitrile and filtered. The supernatant was evaporated to dryness and to the residue water was added and solid collected (30 mg, 43%). m.p. 232-234 C, , ^{1}H NMR (TFA) : 9.26 (s, 1H), 8.37 (S, 1H), 5.78-5.58 (m, 1H), 4.85-4.1 (m, 5H), 3.0-2.7 (m, 5H), 2.68 (s, 3H), 1.65-1.15 (m, 4H). Anal. calcd. for $C_{21}H_{21}F_2N_5O_3$; C, 58.74; H, 4.93; N, 16.31. Found ; C, 58.14; H, 5.06; N, 16.08.

Example 22

1-Cyclopropyl-6,8-difluoro-7-[3-(1,2,3-triazol-1-yl) azetidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic

acid

1-Cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (50 mg, 0.18 mmole) was reacted with 3-(1,2,3-triazol-1-yl)azetidine hydrochloride (72 mg, 0.45 mmole) in 3 ml of dry pyridine in the presence of 68.5 mg (0.45 mmole) of DBU at 80 C for 16 hr. The yellow solution was then evaporated to dryness, and water was added to the residue and solid was collected and dried to yield 64 mg (92%) of the desired product. m.p. 315-316°C, ^{1}H NMR (TFA), 9.26 (s, 1H), 8.75 (d, 1.2 Hz, 1H), 8.60 (d, 1.3 Hz, 1H), 8.10 (d, 11.8 Hz, 1H), 6.35-6.0 (m, 1H), 5.8-5.15 (m, 4H), 4.65-4.3 (m, 1H), 1.9-1.3 (m, 4H). Anal. calcd. for $C_{18}H_{15}F_2N_5O_3$ H_2O; C, 53.33; H, 4.23; N, 17.28; found; C, 53.68; H, 4.23; N, 17.28.

Example 23

5-Amino-1-cyclopropyl-6,8-difluoro-7-[3-(1,2,4-triazol-1-yl)azetidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

A suspension of 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (75 mg, 0.25 mmole) and 100 mg (0.5 mmole) of 3-(1,2,4-triazol-1-yl)azetidine hydrochloride in 3 ml of dry pyridine, in the presence of 152 mg (1 mmole) of DBU was heated under nitrogen at 75°C overnight. The suspension was then evaporated to dryness and to the residue water was added and solid collected, washed with water and dried to give 95 mg (94%) of the desired product as a yellow solid, m.p. 293-295°C. ^{1}H NMR (TFA) : 9.79 (s, 1H), 9.1 (s, 1H), 8.88 (s, 1H), 6.12-5.88 (m, 1H), 5.45-5.05 (m, 4H), 4.44-4.16 (m, 1H), 1.53-1.18 (m, 4H). Anal. calcd. for $C_{18}H_{16}F_2N_6O_3$; C, 53.74; H, 4.01; N, 20.88; Found; C, 53.60; H, 4.08; N, 20.91.

Example 24

1-Cyclopropyl-6,8-difluoro-7-[3-(5-methyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

To 100 mg (0.36 mmole) of 1-Cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 166 mg (0.9 mmole) of 3-(5-methyl-1,2,3-triazol-1-yl) pyrrolidine hydrochloride in 10 ml of pyridine was added 134 mg (0.9 mmole) of DBU and the resulting solution was heated under nitrogen at 120°C for 3 days. The very fine suspension was then filtered and evaporation of the supernatant afforded a residue which was crystallized upon addition of water. The solid was collected (117 mg), m.p. 199-200°C. ^1H NMR ($CDCl_3$) : 8.73 (s, 1H), 7.83 (d, 13.7 Hz, 1H), 7.5 (s, 1H), 5.1-4.9 (m, 1H), 4.48-3.88 (m, 5H), 2.77-2.45 (m, 2H), 2.4 (s, 3H), 1.4-1.1 (m, 4H). Anal. calcd. for $C_{20}H_{19}F_2N_5O_3H_{20}$; C, 55.42; H, 4.88; N, 16.16; Found; C, 55.64; H, 4.49; N, 15.73.

Example 25

1-Cyclopropyl-6,8-difluoro-5-methyl-7-[3-(1,2,4-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

1-Cyclopropyl-5-methyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (30 mg, 0.1 mmole) was reacted with 40 mg (0.2 mmole) of 3-(1,2,4-triazol-1-yl)pyrrolidine hydrochloride in 2 ml of pyridine in the presence of 70 mg (0.45 mmole) of DBU at 95°C overnight. The orange solution was evaporated to dryness and to the residue water was added. The orange solid was collected and washed with methanol to yield 19 mg of the crude product, which upon further purification from methanol yielded 12 mg of the desired product, m.p. 207-210°C. ^1H NMR (TFA) : 9.81 (s, 1H), 9.27 (s, 1H), 8.78 (s, 1H), 5.75-5.55 (m, 1H), 4.83-4.12 (m, 5H), 3-2.7 (m, 5H), 1.7-1.2 (m, 4H). Anal. calcd. for $C_{20}H_{19}F_2N_5O_3 \cdot H_2O$; C, 55.43; H, 4.88; N, 16.16; Found; C, 55.72; H, 4.73; N, 15.65.

Example 26

1-Cyclopropyl-6,8-difluoro-5-methyl-7-[3-(1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

1-Cyclopropyl-5-methyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (30 mg, 0.1 mmole) was reacted with 35 mg (0.2 mmole) of 3-(1,2,3-triazol-1-yl)pyrrolidine hydrochloride in 2 ml of dry pyridine under nitrogen in the presence of 30.4 mg (0.2 mmole) of DBU under reflux conditions. The solvent was removed under reduced pressure and to the orange viscous oil water was added and the solid was collected which was further purified from methanol to yield 20 mg of the desired product, m.p. 228-230°C. ^{1}H NMR (TFA) : 9.28 (s, 1H), 8.68 (s, 1H), 8.57 (d, 1.4 Hz, 1H), 5.9-5.75 (m, 1H), 4.88-4.14 (m, 5H), 3.1-2.72 (m, 5H), 1.7-1.2 (m, 4H).

Example 27

5-Amino-1-cyclopropyl-6,8-difluoro-7-[3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

5-Amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (298 mg, 1 mmole) was reacted with 470 mg (2.5 mmole) of 3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine hydrochloride in the presence of 380 mg (2.5 mmole) of DBU in 20 ml of dry acetonitrile for two days under reflux conditions under the atmosphere of nitrogen. The yellow suspension was then evaporated to dryness and to the residue water was added. The yellow solid was filtered and crystallized repeatedly (3x) with acetonitrile to free the product from the unreacted starting material. After drying, 200mg of the desired product was obtained, m.p. 271-272.5°C. ^{1}H NMR (TFA) : 9.15 (s, 1H), 8.4 (s, 1H), 5.8-5.6 (m, 1H), 4.8-4.05 (m, 5H), 3.0-2.7 (m, 2H), 2.67 (s, 3H), 1.65-1.2 (m, 4H). Anal. calcd. for $C_{20}H_{20}F_2N_6O_3 \cdot 1/2\ H_2O$; C, 54.67; H, 4.82; N, 19.12; Found; C, 54.91; H, 4.69; N, 18.76.

Example 28

1-Cyclopropyl-6,8-difluoro-7[3-(4,5-dimethyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

1-Cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (100 mg, 0.36 mmole) was reacted with 3-(4,5-dimethyl-1,2,3-triazol-1-yl)pyrrolidine hydrochloride (182 mg, 0.9 mmole) in 8 ml of dry pyridine in the presence of 137 mg (0.9 mmole) of DBU at 115 C for five days. The small amounts of the solid was filtered off and the supernatant was evaporated to dryness. To the residue water and few drops of acetonitrile was added. The solid was collected to afford after drying 125 mg (81%) of the desired product as a gray solid, m.p. 230-232°C (dec). ^{1}H NMR ($CDCl_3$) : 8.74 (s, 1H), 7.84 (d, J=13.2 Hz, 1H), 5.07-4.8 (m, 1H), 4.4-3.85 (m, 5H), 2.8-2.14 (m, 8H, singlet at 2.29, 6H), 1.4-1.0 (m, 4H).

Anal Calcd. for $C_{21}H_{21}F2N_5O_3$ 1/2 H_2O; C, 57.52; H, 4.83; N, 15.97; Found; C, 57.68; H, 4.81; 15.68.

Example 29

1-Cyclopropyl-6,8-difluoro-7-[3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

1-Cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (150 mg, 0.53 mmole) was reacted with 249 mg (1.33 mmole) of 3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine hydrochloride in the presence 201 mg (1.33 mmole) of DBU in 15 ml of dry pyridine under nitrogen at 120°C for 3 days. Small amounts of the solid present were removed by filtration, and the supernatant was concentrated under reduced pressure. Water and small amounts of acetonitrile were added to the residue and the grey solid was collected and dried to afford 180 mg (82%) of the desired product, m.p. 219-220°C. ^{1}H NMR ($CDCl_3$) : 8.73 (s, 1H), 7.85 (dd, J=13.7, 1.9 Hz, 1H), 7.42 (s, 1H), 5.4-5.3 (m, 1H), 4.4-3.7 (m, 5H), 2.7-2.5 (m, 2H), 2.37 (s, 3H), 1.4-1.05 (m, 4H). Anal. calcd. for $C_{20}H_{19}F_2N_5O_3$; C, 57.83; H, 4.57; N, 16.86; Found; C, 57.81; H, 4.60; N, 16.31.

Example 30

5-Amino-1-cyclopropyl-6,8-difluoro-7-[3-(1,2,4-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

To a suspension of 60 mg (0.2 mmole) of 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 80 mg of 3-(1,2,4-triazol-1-yl)pyrrolidine hydrochloride in 3 ml of dry pyridine under N_2 was added 140 mg (0.9 mmole) of DBU, and the suspension was heated at 95°C for 22 hr. The resulting orange solution was then evaporated to dryness, water was added to the residue, and the orange solid was collected and washed with methanol to give after drying 50 mg (60%) of yellowish solid, m.p. 240.3-242.3°C. ^{1}H NMR (TFA) : 9.8 (s, 1H), 9.14 (s, 1H), 8.77 (s, 1H), 5.78-5.55 (m, 1H), 4.76-4.12 (m, 5H), 2.9-2.65 (m, 2H), 1.65-1.2 (m, 4H). Anal. calcd. for $C_{19}H_{18}F_2N_6O_3$; C, 54.81; H, 4.36; N, 20.17; Found; C, 54.52; H, 4.44; N, 20.00.

Example 31

5-Amino-1-cyclopropyl-6,8-difluoro-7-[3-(1,2,3-triazol-1-yl)azetidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

A solution of 75 mg (0.25 mmole) of 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 3-(1,2,3-triazol-1-yl)azetidine hydrochloride (99.7 mg, 0.625 mmole) in 3 ml of pyridine in the presence of 95 mg of DBU was heated at 75°C overnight. The resulting suspension was evaporated to dryness and to the residue water was added and the yellow solid collected (99 mg, 98%), m.p. >330°C (dec). ^{1}H NMR (TFA) : 9.1 (s, 1H), 8.74 (s, 1H), 8.6 (s, 1H), 6.2-5.98 (m, 1H), 5.55-5.05 (m, 4H), 4.45-4.15 (m, 1H), 1.65-1.2 (m, 4H). Anal. calcd. for $C_{18}H_{16}F_2N_6O_3$; C, 53.74; H, 4.01; N, 20.88; Found; C, 53.63; H, 3.99; N, 20.20.

Example 32

1-Cyclopropyl-6,8-difluoro-7-[3-(1,2,4-triazol-1-

yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

To a solution of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (70.75 mg, 0.25 mmole) and 3-(1,2,4-triazol-1-yl)pyrrolidine-1-yl hydrochloride (100 mg) in 3 ml of dry pyridine under N_2 was added 152 mg (1 mmole) of DBU and the solution was heated at 95°C overnight. The orange solution was then concentrated under reduced pressure and water was added to the residue and the solid was collected and dried to yield 50 mg (50%) of a gray solid, m.p. 219.7-220.7°C. ^{1}H NMR (TFA) : 9.8 (s, 1H), 9.29 (s, 1H), 8.78 (s, 1H), 8.11 (d, J=12.5, 1H), 5.85-5.58 (m, 1H), 4.9-4.2 (m, 5H), 3.00-2.7 (m, 2H), 1.75-1.3 (m, 4H).

Anal. calcd. for $C_{19}H_{17}F_2N_5O_3$; C, 56.86; H, 4.27; N, 17.45. Found; C, 56.80; H, 4.41; N, 17.48.

Example 33

1-Cyclopropyl-6,8-difluoro-7-[3-(1,2,4-triazol-1-yl)pyrrolidin-1-yl]-1,4-dihdyro-4-oxoquinoline-3-carboxylic acid methanesulfate

1-Cyclopropyl-6,8-difluoro-7-[3-(1,2,4-triazol-1-yl)pyrrolidin-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (20 mg, 0.05 mmole) was dissolved in 2 ml of chloroform and to this was added 4 ml of methansulfonic acid in chloroform. The suspension formed was stirred at room temperature for five hr. The solid was collected to yield 12 mg of white solid after drying very well in the oven, m.p. 208.5-210°C. ^{1}H NMR (CD_3OD) : 9.54 (s, 1H), 8.78 (s, 1H), 8.64 (s, 1H), 7.81 (dd, 13.8, 2.3 Hz, 1H), 5.47-5.3 (m, 1H), 4.5-3.8 (m, 5H), 2.88-2.5 (m, 5H, singlet at 2.7), 1.4-1.1 (m, 4H).

Anal. calcd. for $C_{20}H_{21}F_2N_5O_6S \cdot H_2O$; C, 46.60; H, 4.50; N, 13.59. Found; C, 46.75; H, 4.38; N, 13.51.

Example 34

1-Cyclopropyl-6-fluoro-7-[3S-(1,2,3-triazol-1-yl)pyrrolidine-1-yl]-8-methoxy-1,4-dihydro-4-

oxoquinoline-3-carboxylic acid

To 50 mg (0.15 mmole) of ethyl 6,7-difluoro-1-cyclopropyl-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylate was added 1 ml of fluoroboric acid (50% in water) and the mixture was heated at 90-100°C for 3 hr. The solution was then poured into water and solid collected (60 mg). The white solid was dissolved in 1 ml of DMSO and to this solution was added 52 mg (0.3 mmol) of 3S-(1,2,3-triazol-1-yl)pyrrolidine hydrochloride and 46 mg (0.3 mmol) of DBU. The mixture was then heated at 90°C for 42 hr. The reaction mixture was cooled to room temperature and water was added and solid collected. This solid was dissolved in 8 ml of 80% methanol and 0.25 ml of triethylamine was added and refluxed for 4 hr. The solution was cooled and the few particles were filtered. The supernatant was evaporated to dryness, and to the ethanol was added to the residue, the solid collected, washed with ether and dried to yield 10 mg of the desired product, m.p. 195-197°C. ^{1}H NMR (TFA) : 9.34 (s, 1H), 8.68 (s, 1H), 8.57 (d, 1H), 8.09 (d, 13.2 Hz, 1H), 5.95-5.8 (m, 1H), 4.85-4.3 (m, 4H), 4.2-4.0 (m, 1H), 3.79 (s, 3H), 3.1-2.7 (m, 2H), 1.7-1.1 (m, 4H).

Example 35

1-Cyclopropyl-6-fluoro-7-[3-(1,2,3-triazol-1-yl)pyrrolidine-1-yl]-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

Ethyl6,7-difluoro-1-cyclopropyl-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylate was complexed with fluorobic acid according to the procedure described in Example 34, and then reacted with 3-(1,2,3-triazol-1-yl)pyrrolidine under the same reaction conditions, followed by hydrolysis to yield the desired product, m.p. 200-201°C. ^{1}H NMR (TFA) : 9.34 (s, 1H), 8.69 (d, 1H), 8.58 (d, 1H), 8.09 (d, 13.3 Hz, 1H), 5.93-5.8 (m, 1H), 4.83-4.34 (m, 4H), 4.2-4.0 (m, 2H), 3.79 (s, 3H), 3.05-2.75 (m, 2H), 1.7-1.1 (m, 4H). Anal. calcd. for $C_{20}H_{20}FN_5O_4 \cdot 1/2\ H_2O$; C, 56.87; H, 5.01; N, 16.58; Found: C, 56.86; H, 4.68; N, 16.24.

Example 36

1-Cyclopropyl-6-fluoro-7-[3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

The borane complex prepared according to the Example 34 is reacted with 3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine and the resulting conjugated product was subjected to the same hydrolysis procedure to yield 10 mg of the desired product, m.p. 174-176°C. ^{1}H NMR (TFA) : 9.34 (s, 1H), 8.39 (s, 1H), 8.08 (d, 13.4 Hz, 1H), 5.84-5.16 (m, 1H), 4.78-4.18 (m, 4H), 4.2-4.0 (m, 1H), 3.78 (s, 3H), 3.08-2.7 (m, 2H), 2.67 (s, 3H), 1.75-1.05 (m, 4H). Anal. calcd. for $C_{21}H_{22}FN_5O_4 \cdot 1\ 1/2\ H_2O$; C, 55.50; H, 5.54; N, 15.41. Found; C, 55.73; H, 4.95; N, 14.63.

Example 37

1-Cyclopropyl-6-fluoro-7-[3-(1,2,4-triazol-1-yl)pyrrolidin-1-yl-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

The borane complex of ethyl 6,7-difluoro-1-cyclopropyl-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylate (50 mg) was formed according to the procedure described for Example 34, and reacted in the same manner with 3(1,2,4-triazol-1-yl)pyrrolidine hydrochloride. The product from this reaction was then hydrolyzed using triethylamine as described in example 31 to yield the desired product, m.p. 221-222°C. ^{1}H NMR (TFA) : 9.82 (s, 1H), 9.34 (s, 1H), 8.79 (s, 1H), 8.08 (d, 13.3 Hz, 1H), 5.85-5.64 (m, 1H), 4.8-4.3 (m, 4H), 4.25-4.0 (m, 1H), 3.81 (s, 3H), 3.0-2.7 (m, 2H), 1.7-1.1 (m, 4H).

Example 38

N,N,N-Trimethyl-N-(2-hydroxyethyl) ammonium 1-cyclopropyl-6,8-difluoro-7-[3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylate

To a suspension of 1-cyclopropyl-6,8-difluoro-7-[3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-

oxoquinoline-3-carboxylic acid (415.4 mg, 1 mmole) in 2.5 ml of methanol and 0.8 ml water at room temperature was added slowly 0.31 ml of 45% N,N,N-trimethyl-2-hydroxy-ethyl-ammonium hydroxide in methanol (1 mmole). The solution was stirred at room temperature for an additional hour. This was filtered through small amount of cotton and the supernatant was evaporated under reduced pressure at 30°C. The residue was crystallized from acetone-methanol to yield after drying 420 mg of off-white solid, m.p. 188.7-190.7°C. ^{1}H NMR (D_2O) : 8.44 (s, 1H), 7.84 (bs, 1H), 7.62 (bd, 13.9 Hz, 1H), 5.43-5.22 (m, 1H), 4.35-3.62 (m, 7H), 3.52 (t, 2H), 3.21 (s, 9H), 2.73-2.16 (m, 5H, singlet at 2.29), 1.74-0.9 (m, 4H). Anal. calcd. for $C_{25}H_{32}F_2N_6O_4$ 1/2 H_2O; C, 56.98; H, 6.31; N, 15.94. Found; C, 56.76; H, 6.26; N, 15.43.

Example 39

N-(2-Hydroxyethyl)ammonium-1-cyclopropyl-6,8-difluoro-7[3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylate

A suspension of 20 mg (0.05mmole) of 1-cyclopropyl-6,8-difluoro-7[3-[4-methyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid in 2ml of ethanol was reacted with 3.054 mg (0.05m mole) of the ethanolamine at room temperature for 2 hr. Additional equivalent of ethanolamine was added and the reaction mixture was stirred overnight. The solid was then collected,, mp. 215.1-216.8°C. ^{1}H NMR (D20) : 8.46 (s,1H), 7.86 (bs,1H), 7.68 (bd,14Hz,1H), 5.46-5.25 (m,1H), 4.4-3.7 (m,7H), 3.17-3.07 (m,2H), 2.76-2.2 (m,5H,singlet at 2.31), 1.3-1 (m,4H). Anal. calcd. for $C_{22}H_{26}F_2N_6O_4.H_2O$; C, 53.44; H, 5.71; N, 16.99. Found; C, 53.68; H, 5.93; N, 16.48.

Example 40

N,N,N-Trimethyl-N-(2-hydroxyethyl)ammonium 1-cyclopropyl-6,8-difluoro-7-[3-(1,2,4-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylate

To a suspension of 100.25 mg (0.25mmole) of 1-cyclopropyl-6,8-difluoro-7(3-([4-methyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid in 0.625 ml of methanol and 0.2 ml water was added at room temperature slowly 0.075 ml of 45% choline in methanol. The solution ws stirred at room temperature for an additional hour and after being through a cotton filter, the supernatant was evaporated to dryness under reduced pressure (30°C). The residue was crystallized from acetone-methanol and dried to give 85 mg of off white solid, mp. 193-194.2°C. ^{1}H NMR (CD3OD) : 8.61 (s,1H), 8.42 (bs,1H) 8.01 (s,1H), 7.76 (dd,14,1.8Hz,1H), 5.3-5.15 (m,1H), 4.3-3.75 (m, 7H), 3.5-3.44 (m, 2H), 3.21 (s, 9H), 2.62-2.45 (m, 2H), 1.22-1.02 (m, 4H). Anal. calcd. for $C_{24}H_{30}F_2N_6O_4$ H_2O; C, 55.16; H, 6.13; N, 16.07. Found; C, 54.46; H, 5.91; N, 15.82.

Example 41

(-)-9-Fluoro-3(S)-methyl-10-[3-(1,2,3-triazol-1-yl)pyrrolidine-1-yl]-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

To a suspension of 76 mg (0.27 mmole) of (-)-9,10-difluoro-3(S)-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid and 118 mg (0.675 mmole) of 3-(1,2,3-triazol-1-yl)pyrrolidine hydrochloride in 10 ml of dry acetonitrile was added 121 mg (0.81 mmole) of DBU. The reddish brown solution was refluxed for 31 hr. The solvent was then removed under reduced pressure. To the residue water was added and extracted with chloroform. The organic layer was then evaporated to dryness, and to the residue water was added and solid collected to yield 10 mg of the desired product, m.p. 225-229°C. ^{1}H NMR (TFA) : 9.17 (s, 1H), 8.67 (s, 1H), 8.57 (s, 1H), 7.99 (d, 13.3 Hz, 1H), 5.9-5.18 (m, 1H), 5.22-4.07 (m, 7H), 3.13-2.63 (m, 2H), 1.82 (s, 3H), 1.79 (s, 3H). Anal. calcd for $C_{19}H_{18}N_5O_4F \cdot 1/2$ H_2O; C, 55.86; H, 4.69; N, 17.16. Found; C, 55.93; H, 4.59; N, 16.37.

Example 42

(-)-9-Fluoro-3(S)-methyl-10-[3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine-1-yl]-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

A solution of 70.25 mg (0.25 mmole) of (-)-9,10-difluoro-3(S)-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid and 141 mg (0.75 mmole) of 3(4-methyl-1,2,3-triazol-1-yl)pyrrolidine hydrochloride in 3 ml of acetonitrile in the presence of 152.24 mg (1 mmole) of DBU was refluxed for 3 days under nitrogen atmosphere. The suspension was then evaporated and water was added to the residue and solid collected and washed with methanol to yield after drying 50 mg of the desired product, m.p. 241-242°C. ^{1}H NMR (TFA) : 9.16 (s, 1H), 8.37 (s, 1H), 7.99 (d, 13.3 Hz, 1H), 5.75-5.6 (m, 1H), 5.15-4.1 (m, 7H), 3-2.6 (m, 5H, singlet at 2.67), 1.8 (d, 6.8 Hz, 3H). Anal. calcd. for $C_{20}H_{20}FN_5O_4 \cdot 1/2\ H_2O$; C, 56.87; H, 5.01; N, 16.58. Found; C, 57.30; H, 4.77; N, 16.75.

Example 43

(-)-9-Fluoro-3-(s)-methyl-10-[3-(1,2,4-triazol-1-yl)pyrrolidine-1-yl]-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]1,4-benzoxazine-6-carboxylic acid

A suspension of 70.25 mg (0.25 mmole) of (-)-9,10-difluoro-3(S)-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid and 87 mg (0.5 mmole) of 3(1,2,4-triazol-1-yl)pyrrolidine hydrochloride in 3 ml of acetonitrile in the presence of 76 mg (0.5 mmole) DBU was stirred under nitrogen at reflux condition overnight. The yellow solution was then evaporated to dryness and to the residue water was added and solid collected. The off-white solid was dissolved in chloroform and the small amounts of the suspension were filtered off. The supernatant was evaporated and to the residue water was added and solid collected (60 mg), m.p. 229-231°C. ^{1}H NMR ($CDCl_3$) : 8.59 (s, 1H), 8.26 (s, 1H), 7.98 (s, 1H), 7.7 (d, 13.5 Hz, 1H), 5.17-5.00 (m, 1H),

4.6-3.73 (m, 7H), 2.67-2.4 (m, 2H), 1.61 (d, 6.7 Hz, 3H).

Example 44

5-Amino-1-cyclopropyl-6,8-difluoro-7-(3-(4-amino-1,2,3-triazol-1-yl)-pyrrolidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (100 mg, 0.67 mmol), 3(4-amino-1,2,3-triazol-1-yl)pyrrolidine dihydrochloride (185 mg, 0.83 mmol) and diazabicyclo-undecane (127 mg, 0.83 mmol) in pyridine (3 ml) was heated at 110°C for 24 hrs. Reaction mixture was concentrated to dryness under vacuum and the solid residue was dissolved in water, extracted with methylene chloride, dried over sodium sulfate and concentrated to dryness. The solid residue thus obtained was crystallized from chloroform to brown solid. Yield 15 mg (10.4%) m.p. 210-213°C. ^{1}H NMR (TFA) : 1.22-1.58 (m, 4H), 2.70-2.90 ((m, 2H), 4.06-4.54 (m, 5H), 5.48-5.60 (m, 1H), 7.79 (s, 1H), 9.14 (s, 1H) ppm.

Example 45

1-Cyclopropyl-6,8-difluoro-7-(3-(4-amino-1,2,3-triazol-1-yl)-pyrrolidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 1-cyclopropyl-6,7,8-trifluoro quinolone-3-carboxylic acid (75 mg, 0.26 mmol), 3(4-amino-1,2,3-triazol-1-yl)pyrrolidine (145 mg, 0.65 mmol) and diazabicycloundecane (198 mg, 1.30 mmol) in acetonitrile (5 ml) heated for 3 days at 110°C. Separated light brown solid was filtered, washed with water and then crystallized from methanol to 55 mg (50.9%) of title compound. m.p. 221°C, NMR (TFA) : 1.38-1.72 (m, 4H), 2.66-2.98 (m, 2H), 4.10-4.80 (m, 5H), 5.42-5.64 (m, 1H), 7.7-7.9 (m, 1H), 9.28 (s, 1H).

Example 46

1-Cyclopropyl-6,8-difluoro-7-(3-(5-carboxy-1,2,3-triazol-

1-yl)-pyrrolidin-1-yl)-1-4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 5-amino, 1-cyclopropyl 6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxalic acid (100 mg, 0.33 mmol), 3(5-ethoxy-carbonyl-1,2,3-triazol-1-yl)-pyrrolidine hydrochloride (178 mg, 0.83 mmol) and diazabicycloundecane (127 mg, 0.83 mmol) was heated at 110°C for 24 hrs., concentrated, diluted with water and the separated solid was washed with water and acetonitrile. The solid was dried in air and redissolved in methanol (5 ml) and to it NaOH (20 mg) in water (5 ml) was added. The solution was heated at 90°C for 6 hrs, cooled and pH lowered using 1N HCl to 4. The separated solid was filtered, recrystallized from methanol/ether, yield 20 mg (13.98%), m.p. 214°C, NMR : 1.30-1.62 (m, 4H), 2.70-3.0 (m, 2H), 3.74-4.80 (m, 5H), 5.60-5.70 (m, 1H), 8.86 (s, 1H), 9.14 (s, 1H).

Example 47

1-cyclopropyl-6,8-difluoro-7-[3-(5-aminomethyl(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-6-oxo-quinoline-3-carboxylic acid

A mixture of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline (200 mg, 0.706 mmol) and 5-amino methyl-(1,2,3-triazol-1-yl)-pyrrolidine dihydrochloride (585 mg, 2.46 mmol) and diazabicyclo undecane (325 mg, 2.48 mmol) in pyridine (8 ml) was heated at 110°C for 20 hrs, concentrated and the residue washed repeatedly with acetonitrile. The solid thus obtained was redissolved in chloroform and then washed with water, brine and dried using anhyd. sodium sulfate. Evaporation of chloroform yielded 120 mg (40.33%) of desired product, m.p. 138°C. (TFA) : 1.30-1.70 (m, 4H), 2.72-3.05 (m, 2H), 4.20-4.67 (m, 5H), 4.73-4.95 (m, 1H), 5.15 (s, 2H), 5.93-6.17 (m, 1H), 8.12 (d, 1H), 8.88-9.30 (s, 1H).

Example 48

1-cyclopropyl-6,8-difluoro-7-[3(4-carboxyl-1,2,3-triazol-

1-yl)pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (140 mg, 0.49 mmol), 3(4 carboxy-1,2,3-triazol-1-yl)pyrrolidine hydrochloride (269 mg, 1.23 mmol) and diazobicycloundecane (187 mg, 1.23 mmol) in acetonitrile 5 ml was heated at 80-90°C. for four days. The reaction mixture was concentrated diluted with water (10 ml) and pH brought down to 4.0 using 1M HCl. The separated solid was filtered and washed with water and crystallized from MeOH/ether to yellow solid. Yield 29 mg (13.2%), m.p. 222-225°C. ^{1}H NMR ($CDCl_3$ + CD_3OD) : 1.11-1.42 (m, 4H), 3.88-4.30 (m, 4H), 4.40-4.48 (m, 1H), 5.35-5.55 (m, 1H), 7.8 (d, 1H), 8.41 (s, 1H), 8.79 (s, 1H).

Example 49

1-cyclopropyl-6,8-difluoro-7-[3-(4-phenyl-1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (150 mg, 0.53 mmol), 3(4-phenyl-1,2,3-triazol-1-yl) pyrrolidine hydrochloride (252 mg, 1.05 mmol) and diazabicycloundecane (160 mg, 1.05 mmol) in pyridine (5ml) was heated at 110°C for 20 hrs, concentrated, and diluted with water. The separated solid was filtered, washed with water and crystallised from methanol. Yield (55 mg, 22.3%) m.p. 241.5°C. ^{1}H NMR (TFA) : 1.34-1.73 (m, 4H), 2.82-3.09(m, 2H), 4.20-4.95 (m, 5H), 5.73-5.92 (m, 1H), 7.5-7.92 (m, 4H), 8.15 (d, 1H), 8.80 (s, 1H), 9.30 (s, 1H).

Example 50

5-amino-1-cyclopropyl-6,8-difluoro-7-[3-(4-phenyl-1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (100mg, 0.33mmol), 3-(4-phenyl-1,2,3-triazol-1-yl)pyrrolidine

hydrochloride (160mg, 0.42mmol) and diazabicyclo undecane (102mg, 0.67mmol) in pyridine (5 ml) was heated at 90°C for 20 hrs. The reaction mixture was concentrated and the residue was diluted with water. The separated solid was filtered, washed with water, methanol and then with $CHCl_3$ followed by acetonitrile to get 16 mg (10%) of title compound. m.p. 265°C. ^1H NMR (TFA) : 0.92-1.43 (m, 4H), 2.51-2.80 (m, 2H), 3.57-4.59 (m, 5H), 5.43-5.62 (m, 1H), 7.44 (dd, 5H), 8.50 (s, 1H), 8.84 (s, 1H).

Example 51

1-cyclopropyl-6,8-difluoro-5-methyl-7-[3-(4-phenyl-1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of 1-cyclopropyl-6,7,8-trifluoro-5-methyl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (100 mg, 0.37 mmol), 3(-4-phenyl-1,2,3-triazol-1-yl)-pyrrolidine hydrochloride (160 mg, 0.67 mmol) and diazabicycloundecane (102 mg, 0.67 mmol) in (5ml) pyridine was heated at 90°C for 24 hrs. The reaction mixture was concentrated and diluted with water. The separated solid was filtered and washed with water followed by ether and was crystallized from methanol. Yield 89 mg (55%), m.p. 221.4°C. ^1H NMR (TFA) : 1.20-1.70 (m, 4H), 2.76-3.80 (m, 2H), 4.20-4.96 (m, 5H), 5.74-5.90 (m, 1H), 7.52 (dd, 5H), 8.70 (s, 1H), 9.27 (s, 1H).

Example 52

1-cyclopropyl-5,6,8-trifluoro-7-[3-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3- carboxylic acid

A mixture of ethyl-1-cyclopropyl-5,6,7,8-tetrafluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylate (150 mg, 0.45 mmol), 3(1,2,3-triazol-1-yl)-pyrrolidine hydrochloride (216 mg, 1.24 mmol) and diazabicycloundecane (189 mg, 1.24 mmol) in pyridine (5 ml) was heated at 100°C for 24 hrs. The reaction mixture was concentrated and water added to it. The separated solid was filtered, dried and crystallized

from $CHCl_3$/EtOH mixture. The 50 mg of ester thus obtained was dissolved in methanol (10 ml) and aqueous NaOH (10 mg in 7 ml water) was added. The mixture was heated under reflux for 4 hrs. The methanol was evaporated and the remaining aqueous solution was acidified to pH 5, the separated white solid filtered, washed with water and dried in air. Yield 22 mg (11%), m.p. 250-253°C. ^{1}H NMR (TFA) : 1.25-1.70 (m, 4H), 2.75-3.10 (m, 2H), 4.18-4.95 (m, 5H), 5.72-5.95 (m, 1H), 8.56 (s, 1H), 8.70 (s, 1H), 9.27 (s, 1H).

Example 53

1-Cyclopropyl-5-hydroxy-6,8-difluoro-7-[-3-(1,2,3-triazol-1-yl)-pyrrolidin-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A mixture of ethyl-1-cyclopropyl-5-hydroxy-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylate (100 mg, 0.30 mmol), 3-(1,2,3-triazol-1-yl)-pyrrolidine hydrochloride (106.42 mg, 0.61 mmol) and diazabicycloundecane (97 mg, 0.63 mmol) in pyridine (3 ml) was heated at 100°C for 24 hr. The reaction mixture was concentrated to dryness and the residue diluted with water. The separated yellow solid was filtered and purified on silica column using $CHCl_3$ as eluant. The purified ester (30 mg) was dissolved in methanol (20 ml) and to it aqueous NaOH (10 mg in 7 ml H_2O) was added. The solution was heated under reflux for 4 hrs. Methanol was evaporated by distillation and the aqueous solution was acidified using 1N HCl. The precipitated solid was collected by filteration, washed with water and dried at 40°C under vacuum. Yield 22 mg (17.25%), ^{1}H NMR (TFA) : 1.25-1.62 (m, 4H), 2.72-3.03 (m, 2H), 4.10-4.86 (m, 5H), 5.72-5.88 (m, 1H), 8.55 (s, 1H), 8.67 (s, 1H), 9.14 (s, 1H).

Example 54

1-Cyclopropyl-6,8-difluoro-7-[3-(1,2,3,4-tetrazol-2-yl) pyrrolidin-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic

acid

A solution of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (28.3 mg, 0.1 mmole), 3-(1,2,3,4-tetrazol-2-yl) pyrrolidine hydrochloride (35.1 mg, 0.2 mmole) and DBU (45.6 mg, 0.3 mmole) in acetonitrile (2 ml) was refluxed under nitrogen for 23 hrs. The solvent was then evaporated to dryness. The residue was diluted with water and extracted with chloroform. The organic extract was dried over Na_2SO_4, concentrated and the residue was crystallized from methanol-water.

Yield 12 mg, m.p. 192-199°C, ^1H NMR ($CDCl_3$): 8.7 (s,1H0, 8.5 (s,1H), 7.8 (dd.1H), 5.6-5.4 (m, 1H), 4.46-3.76 (m, 5H), 2.9-2.45 (m, 2H), 1.35-1.02 (m, 4H).

Example 55

1-Cyclopropyl-6,8-fluoro-7-[3-(1,2,3,4-tetrazol-1-yl) pyrrolidine-1-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid

A solution of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid (42.3 mg, 0.15 mmole), 3-(1,2,3,4-tetrazol-1-yl) pyrrolidine hydrochloride (53 mg, 0.3 mmole) and DBU (68 mg) in acetonitrile (5 ml) was refluxed under nitrogen and stirring for 23 hrs. The reaction mixture was concentrated and the residue was triturated with water. The separated solid was filtered, washed with acetonitrile and dried to yield 28 mg of the product. m.p. 268-270°C, ^1H NMR (TFA) : 9.65 (bs, 1H), 9.28 (s,1H), 8.1 (d, 1H), 5.85-5.65 (m,1H), 4.9-4.15 (m, 5H), 3.0-2.7 (m,2H), 1.70-1.25 (m, 4H), Anal. calcd for $C_{18}H_{16}F_2N_6O_3 \cdot \frac{1}{2} H_2O$: C, 52.56; H, 4.17; N, 20.44; Found C, 52.91; H, 3.84; N, 20.01.

Example 56

1-Cyclopropyl-6,8-difluoro-7-[3-(1,2,3-triazol-1-yl)piperidine-1-yl]-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

To a suspension of 1-cyclo-propyl-6,7,8-trifluoro-1,4-

dihydro-4-oxoquinoline-3-carboxylic acid (50 mg, 0.18 mmole) and 3-(1,2,3-triazol-1-yl)piperidine-1-yl hydrochloride (83 mg, 0.44 mmole) in 3 ml of acetonitrile was added 67 mg (0.44 mmole) of DBU. The solution was heated at reflux under stream of nitrogen for 16 hr. The suspesion was cooled and the solid collected, washed with water dried to yield 50 mg of the title product, m.p. 239-240°C. ^{1}H NMR (TFA): δ 9.35 (S,1H), 8.61 (S,1H), 8.51 (S,1H), 8.16 (d,J-10.6H$_z$,1H), 5.45-515 (m.1H), 4.7-3.55 (m,5H), 2.85-2.05 (m,4H), 1.8-1.3 (m,4H).

Preparation of Intermediates

Example A

N-Benzyl-3-(1,2,3-triazol-1-yl)-pyrrolidine

A solution of N-benzyl-3-azido-pyrrolidine (1.5 g, 0.0074 mol) in acetone was taken in a steel bomb and cooled in dry ice/acetone bath. To this cold solution acetylene (2.5 mg, 0.096 mol) was added under N_2 atmosphere. The sealed steel bomb was then heated in an oil bath at 75° C for 20 h. The vessel was cooled again in dry ice/acetone bath and excess of acetylene released slowly, while the temperature rose to the room temperature (r.t.). The reaction mixture was concentrated to yellow-brown oil. Crude yield: 2.02 g. Crude compound was purified on silica gel column to obtain the title compound as a light yellow-brown oil. Yield: 1.02 g (60%). ^{1}H NMR ($CDCl_3$) : 2.0-3.3 (m, 6H), 3.7 (S, 2H), 5.3 (m, 1H), 7.45 (S, 5H), 7.8 (S, 1H), 7.95 (S, 1H).

Example B

3-(1,2,3-triazol-1-yl)-pyrrolidine hydrochloride

To a solution of N-benzyl-3-(1,2,3-triazol-1-yl) pyrrolidine (1 g, 0.0044 mol), in methanol (50 ml) was added 10% Pd/C (100 mg) and conc. HCl (1 ml). The suspension was hydrogenated at r.t. and 50 psi pressure for 20 h. The Pd/C was removed by filtration and the solution was concentrated. The residue was recrystallized from methanol/ether to obtain white crystalline title compound. Yield: 680 mg (89.46%). ^{1}H NMR (D_2O) : 2.40-2.80 (m, 2H), 3.58-3.66 (m, 2H), 3.90-3.92 (d, 2H), 5.58-

5.67 (m, 1H), 8.02 (d, 1H), 8.26 (d, 1H).

Example C

N-(tert-butyloxycarbonyl)-3S-(1,2,3-triazol-1-yl)-pyrrolidine

A solution of N-(tert-butyloxy carbonyl)-3S-azido pyrroline (9.1 g, .043 mmol, $[\alpha]^{24}_{D}$ = +40°, MeoH) and acetylene (27 g/mmol) in dry acetone (100 ml) was heated at 75° C for 24 hrs in a pressure reaction vessel. After release of an excess of acetylene, the reaction mixture was concentrated to give 10.1 g of crude oily product. The crude product was purified over silica gel using ethylacetate-hexane (4:1) as eluant. Yield 9.0 g (88%); $[\alpha]^{24}$ D = + 25° (MeOH) ^{1}H NMR ($CDCl_3$) : 1.53 (S, 9H), 2.53 (m, 2H), 3.80 (m, 4H), 5.26 (m, 1H), 7.70 (S, 1H), 7.80 (S, 1H).

Example D

N-(tert-butyloxycarbonyl)-3R-(1,2,3-triazol-1-yl)-pyrrolidine

Prepared by the same procedure as described in Example C from reaction of N-(tert-butyloxy carbonyl)-3R-azide pyrrolidine ($[\alpha]^{24}_{D}$ = -37°, MeOH) and acetylene. Yield 91%, $[\alpha]_D^{24}$=25° (MeOH), ^{1}H NMR ($CDCl_3$) : 1.50 (S, 9H), 2.50 (m, 2H), 3.80 (m, 4H), 5.26 (m, 1H), 7.63 (S, 1H), 7.76 (S, 1H).

Example E

3S-(1,2,3-triazol-1-yl)-pyrrolidine hydrochloride

A solution of N-(tert.-butyloxy carbonyl)-3S-(1,2,3-triazol-1-yl)pyrrolidine (1.0 g, 4.2 mmol) in 20 ml methanol and 2.5 ml of conc. HCl was stirred at room temperature for 30 minutes. The reaction mixture was concentrated and the residue was crystallized from methanol : ether to give 800 mg of the title compound as hydrochloride. $[\alpha]^{24}_{D}$ = + 8° (MeOH), m.p. 189-92°C; ^{1}H NMR (CD_3OD) : 2.23 (m, 2H), 3.20 (t, 2H), 3.50 (d, 2H), 5.30 (m, 1H), 7.93 (S, 1H), 8.23 (S, 1H).

Example F

3R-(1,2,3-Triazol-1-yl)-pyrrolidine hydrochloride

Prepared by following the same procedure as described in example E from N-(tert. butyloxy carbonyl)-3R-(1,2,3-triazol-1-yl)-pyrrolidine. $[\alpha]^{24}_{D}$ - 8° (MeOH), m.p. 190-193° C; ^{1}H NMR (CD3OD) δ: 2.20 (m, 2H), 3.18 (t, 2H), 3.48 (d, 2H), 5.28 (m, 1H), 7.57 (S, 1H), 7.80 (S, 1H).

Example G

trans-3-Hydroxy-4-(1,2,3-triazol-1-yl)-1-N-(tert-butyloxycarbonyl) pyrrolidine

A solution of trans 3-hydroxy-4-azido-1-N-(tert.-butyloxy carbonyl)pyrroline (3.8 g, 17 mmol) in dry acetone (50 ml) was heated at 75-80° for 40 hrs. After releasing the excess of acetylene, the reaction mixture was concentrated and the residue was purified on silica gel using ethyl acetate as eluant. Yield 3.66 g (87%) m.p. 91-93°, ^{1}H NMR ($CDCl_3$) δ: 1.46 (S, 9H), 3.25-4.25 (m, 5H), 4.83 (m, 1H), 7.63 (S, 1H), 7.70 (S, 1H).

Example H

trans-3-Hydroxy-4-(1,2,3-triazol-1-yl)pyrrolidine hydrochloride

Prepared by following the same procedure as described in example E from trans 3-hydroxy-4-(1,2,3-triazol-1-yl)-1-N-(tert-butyloxy carbonyl) pyrrolidine. Yield 89%, m.p. 170-173° C; ^{1}H NMR (CD_3OD) δ: 3.00-3.80 (m, 4H), 4.33 (m, 1H), 5.00 (m, 1H), 7.66 (S, 1H), 7.96 (S, 1H).

Example I

trans-3-[(Methylsulfonyl)oxy]-4-(1,2,3-triazol-1-yl)-1-N-(tert-butyloxy carbonyl) pyrrolidine

Methane sulfonyl chloride (2.84 g, 24.8 mmole) was added slowly to an ice cooled solution of trans 3-hydroxy-4-(1,2,3-triazol-1-yl)-1-N-(tert. butyloxy carbonyl) pyrrolidine (3.16 g, 12.4 mmol) and triethylamine (4.36 ml, 31.3 mmol) in dry CH_2Cl_2 (10 ml). The reaction mixture was stirred under N_2 at room temperature for 22

hrs and washed with saturated $NaHCO_3$ and brine solution. The dichloromethane layer was dried over Na_2SO_4 and concentrated to give the title product. Yield 4.0 g (97%). ^1H NMR ($CDCl_3$) δ: 1.5 (S, 9H), 3.07 (s, 3H), 4.07 (m, 4H), 5.43 (m, 2H), 7.70 (S, 1H), 7.90 (S, 1H).

Example J

cis-3-Azido-4-(1,2,3-triazol-1-yl)-1-N-(tert-butyloxy-carbonyl) pyrrolidine

A mixture of compound of example I (4.0 g, 0.012 mol), NH_4Cl (0.86 g, 0.016 mol), and sodium azide (4.69 g, 0.072 mole) in a mixture of DMF (32 ml) and water (3.8 mol) was heated at 100° C for 6 hrs. The reaction mixture was diluted with water and extracted with ethylacetate. The ethyl acetate extract was dried over Na_2SO_4 and concentrated. The residue was purified over silica gel using ethyl acetate: hexane (2:1) as eluant. Yield 2.85 (85%). ^1H NMR ($CDCl_3$) : 1.48 (S, 9H), 3.90 (m, 4H), 4.45 (m, 1H), 5.36 (m, 1H), 7.70 (S, 1H), 7.80 (S, 1H).

Example K

cis-3-Amino-4-(1,2,3-triazol-1-yl)-1-N-(tert-butyloxy-carbonyl)-pyrrolidine

A solution of compound of example J (2.85 g) in methanol (75 ml) was hydrogenated under 50 psi hydrogen pressure over 10% Pd/C (1.1 g) at room temperature for 18 hrs. The mixture was filtered through celite and concentrated to give the title compound. Yield 2.6 g (86%) ^1H NMR ($CDCl_3$) : 1.5 (S, 9H), 3.30 (m, 1H), 4.0 (m, 4H), 5.13 (m, 1H), 7.70 (S, 1H), 7.83 (S, 1H).

Example L

cis-3-Amino-4-(1,2,3-triazol-1-yl)pyrrolidine

A solution of compound of example K (1.0 g) in trifluoroacetic acid (4 ml) was stirred at room temperature under nitrogen for 10 minutes and concentrated. The residue was dissolved in methanol and treated with basic resin (ANGA-316) and filtered. The

filtrate was concentrated and purified by column chromatography over neutral alumina using methanol/$CHCl_3$ mixture as solvent. Yield 670 mg.
^1H NMR (CD_3OD) : 2.80 (m, 1H), 3.20-3.80 (m, 5H), 5.10 (m, 1H), 7.75 (S, 1H), 8.0 (S, 1H).

Example M

N-Benzyl-3-(4,5-dimethyl-1,2,3-triazol-1-yl)pyrrolidine

To a solution of N-benzyl-3-azidopyrrolidine (2.02 g, 0.01 mole) in 30 ml of 98% ethanol was added 15 ml of butyne and heated in a sealed steel reaction vessel at 105-100 C for 24 hr. Removal of the solvent under reduced pressure afforded 2.55 g of the crude which contained 50% starting material. Chromatography over silica gel using hexane/ethyl acetate (1:1) as solvent yielded 0.88 g of the desired product. ^1H NMR ($CDCl^3$) : 7.36-7.2 (m, 5H), 4.95-4.8 (m, 1H), 3.7 (s, 2H), 3.2-3.1 (m, 1H), 2.93-2.76 (m, 3H), 2.48-2.3 (m, 2H), 2.24 (s, 3H), 2.21 (s, 3H).

Example N

3-(4,5-Dimethyl-1,2,3-triazol-1-yl)pyrrolidine hydrochloride

To a solution of 0.86 g of N-benzyl-3-(4,5-dimethyl-1,2,3-triazol-1-yl)pyrrolidine in 50 ml of methanol and 2 ml of 1N hydrochloric acid was added 0.5 ml of concentrated hydrochloric acid followed by the addition of 10% Pd/C (0.5 g). The suspension was then hydrogenated at 50 psi pressure overnight. The Pd/C was removed by filtration through celite and the supernatent was evaporated to dryness and crystallized from methanol-ether to yield 0.5 g of the desired product. ^1H NMR (D_2O) : 5.75-5.6 (m, 1H), 4.14-3.9 (m, 2H), 3.8-3.6 (m, 2H), 2.86-2.4 (m, 8H, two singlets at 2.49 and 2.4).

Example O

N-Benzyl-3-(4 and 5-methyl-1,2,3-triazol-1-yl)pyrrolidine
N-Benzyl-3-(5-methyl-1,2,3-triazol-1-yl)pyrrolidine

A solution of 2.02 g (0.01 mole) of N-benzyl-3-azidopyrrolidine and 30 ml of 98% ethanol in a steel

reaction vessel was cooled to -78 C and into this was bubbled 17 g of the propyne. The sealed reaction vessel was then heated at 110°C for 2 1/2 days. Removal of the solvent at reduced pressure resulted in 3 g of the crude product. Purification over silica gel (5% methanol ethyl acetate) afforded in the order of elution, 1.47 g of N-benzyl-3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine. ^{1}H NMR ($CDCl_3$) : 7.54 (s, 1H), 7.42-7.2 (m, 5H), 5.3-5.1 (m, 1H), 3.68 (s, 2H), 3.15-2.75 (m, 3H), 2.65-2.4 (m, 5H, singlet at 2.35) and 0.87 g of N-benzyl-3-(5-methyl-1,2,3-triazol-1-yl)pyrrolidine. 1H NMR ($CDCl_3$) : 7.43 (s, 1H), 7.36-7.22 (m, 5H), 5.02-4.85 (m, 1H), 3.71 (s, 2H), 3.24-3.12 (s, 2H), 3.24-3.12 (m, 1H), 2.95-2.8 (m, 3H), 2.5-2.35 (m, 2H), 2.31 (s, 3H).

Example P

3-(4-Methyl-1,2,3-triazol-1-yl)pyrrolidine hydrochloride

Prepared using the same procedure described in Example N by hydrogenating 1 g of N-benzyl-3-(4-methyl-1,2,3-triazol-1-yl)pyrrolidine. The yellow viscous liquid obtained after evaporation was crystallized from methanol ether to yield 0.82 g of white solid. ^{1}H NMR (D_2O) :8.12 (s, 1H), 5.67-5.55 (m, 1H), 3.95 (d, 5.3 Hz, 2H), 3.67 (d, 6.26 Hz, 1H), 3.63 (d, 6.1 Hz, 1H), 2.85-2.45 (m, 2H), 2.42 (s, 3H).

Example Q

3-(5-Methyl-1,2,3-triazol-1-yl)pyrrolidine hydrochloride

Hydrogenation of 0.87 g of the N-benzyl-3(5-methyl-1,2,3-triazol-1-yl)pyrrolidine according to the procedure described for Example N afforded 0.708 g of the desired product as a white salt after purification from methanol-ether. ^{1}H NMR (D_2O) :7.63 (s, 1H), 5.7-5.5 (m, 1H), 4.25-3.6 (m, 4H), 2.87-2.37 (m, 5H, singlet at 2.51).

Example R

N-Benzhydryl-3-azidoazetidine

To a solution of N-benzhydryl-3-mesyloxyazetidine (5.04 g,

16 mmol) in 180 ml of dimethylformamide and 30 ml of water was added 3.12 g (48 mmol) of sodium azide and 1.87 g (35 mmol) of ammonium chloride. The mixture was heated at 100°C for 20 hr, cooled and diluted with water. This was extracted with methylene chloride and the combined organic layers were washed with water, dried and evaporated to yield 6.49 g of the product (contains some DMF). ^{1}H NMR ($CDCl_3$) :7.40-7.09 (m, 10H), 4.35 (s, 1H), 4.02-3.83 (m, 1H), 3.46-3.12 (m, 2H), 3.05-2.91 (m, 2H).

Example S

N-Benzhydryl-3-(1,2,3-triazol-1-yl)azetidine

To a solution of 1.05 g (3.98 mmol) of N-benzhydryl-3-azidoazetidine in 50 ml of acetone cooled to -78°C in a steel reaction vessel was bubbled 36 g of acetylene. The sealed reaction vessel after warming up to room temperature was heated at 80 C for 17 hr. The solution was then cooled to room temperature, filtered and evaporated to yield the crude prodaww which after chromatography over silica gel (2.5% methanol chloroform) yielded 0.88 g (76%) of the desired product as a solid, m.p. 167-168 C. ^{1}H NMR ($CDCl_3$) :7.88 (s, 1H), 7.73 (s, 1H), 7.55-7.07 (m, 10H), 5.35-5.1 (m, 1H), 4.53 (s, 1H), 3.76 (t, 2H), 3.5 (t, 2H).

Example T

3-(1,2,3-Triazol-1-yl)azetidine hydrochloride

To a mixture of 0.88 g (3.03 mmol) of N-benzhydryl-3-(1,2,3-triazol-1-yl)azetidine in 25 ml of 98% ethanol was added 3 ml of 1N hydrochloric acid. To this solution was added 0.3 g of Pd/C (10%) and the mixture was then hydrogenated at 50 psi for 18 hr. After filtration of the Pd/C, the solvent was removed under reduced pressure, and the residue was crystallized from methanol-ether to yield 0.25 g (51%) of the desired product m.p. 158-160°C. ^{1}H NMR (D_2O) :8.16 (s, 1H), 7.92 (s, 1H), 5.95-5.75 (m, 1H), 4.97-4.65 (m, 4H).

Example U

N-Benzhydryl-3-(1,2,4-triazol-1-yl)azetidine

A suspension of N-benzhydryl-3-mesyloxyazetidine (0.951 g, 3 mmole) and potassium-1,2,4-triazolide (0.69 g, 6.5 mmole) in 50 ml of dimethylformamide was heated at 85-90°C overnight. To this, water (200 ml) was added and extracted with ethyl acetate. The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated to yield 0.9 g of the crude which upon purification over silica gel using ethyl acetate as solvent yielded 0.6 g of the desired product as a white solid. ^1H NMR ($CDCl_3$) :8.22 (s, 1H), 7.97 (s, 1H), 7.57-7.12 (m, 5H), 5.13-4.9 (m, 1H), 4.53 (s, 1H), 3.8-3.4 (m, 4H).

Example V

3-(1,2,4-Triazol-1-yl)azetidine hydrochloride

To a mixture of N-benzhydryl-3-(1,2,4-triazol-1-yl)azetidine (0.6 g) in 20 ml of ethanol was added 2 ml of 1N hydrochloric acid followed by the addition of 0.6 g of Pd/C (10%). The mixture was hydrogenated at 50 psi for two days. After filtration and evaporation, the crude product was crystallized from methanol-ether to afford 0.235 g of white solid. ^1H NMR (D_2O) : 9.14 (s, 1H), 8.57 (s, 1H), 5.97 (m, 1H), 4.8-4.5 (m, 4H).

Example W

N-Benzyl-3-(1,2,4-triazol-1-yl)pyrrolidine

To a solution of 2.55 g (10 mmole) of N-benzyl-3-mesyloxy-pyrrolidine in 100 ml of dimethylformamide was added 3.21 g of potassium-1,2,4-triazolide and the reaction mixture was heated at 85-90°C overnight. The same work up and purification procedure described in Example U afforded 1.32 g (15% methanol-ethyl acetate as solvent) of the title product. ^1H NMR ($CDCl_3$) : 8.3 (s, 1H), 7.93 (s, 1H), 7.6-7.1 (m, 5H), 5.2-4.6 (m, 1H), 3.67 (s, 2H), 3.23-2 (m, 6H).

Example X

3-(1,2,4-Triazol-1-yl)pyrrolidine hydrochloride

The N-benzyl-3-(1,2,4-triazol-1-yl)pyrrolidine (1.3 g) was hydrogenated under similar conditions to Example V for 3 days to yield after crystallization from methanol-ether 1.08 g of white solid. ^1H NMR (D_2O) : 9.24 (s, 1H), 8.51 (s, 1H), 5.68-5.5 (m, 1H), 3.97-3.5 (m, 4H), 2.86-2.4 (m, 2H).

Example Y

N-benzyl-3(4-ethoxy-carbonyl-1,2,3-triazol-1-yl)pyrrolidine and N-benzyl-3(-5-ethoxy-carbonyl-1,2,3-triazol-1 yl)pyrrolidine

A mixture of N-benzyl-3-azido-pyrrolidine (5 g, 0.024 mmol) and Ethyl-propolate (5 g, 0.051 mmol) in benzene (50 ml) heated under reflux for 48 hrs. Reaction solution was evaporated to dark brown oil, purified on silica gel column using ethylacetate, $CHCl_3$ and methanol to get N-benzyl-3-(5-ethoxy-carbonyl-1,2,3-triazol-1-yl)pyrrolidine (1.5 g, 20.6%). NMR ($CDCl_3$) : 1.37 (t, 3H), 2.42-2.58 (m, 2H), 2.71-3.01 (m, 3H), 3.20-3.32 (m, 1H), 3.73 (s, 2H), 4.35 (q, 2H), 5.72-5.88 (m, 1H), 7.2-7.4 (m, 5H), 8.12 (s, 1H). N-benzyl-3-(4-ethoxyl-carbonyl-1,2,3-triazol-1-yl)pyrrolidine (5 g, 68.7%). NMR ($CDCl_3$) : 1.40 (t, 3H), 1.8-3.20 (m, 6H), 3.70 (s, 2H), 4.40 (q, 2H), 5.06-5.48 (m, 1H), 7.33 (s, 5H), 8.43 (s, 1H).

Example Z

N-benzyl-3-(4-carboxy-1,2,3-triazol-1-yl)pyrrolidine hydrochloride

A solution of N-benzyl-3-(4-ethoxy-carbonyl-1,2,3-triazol-1-yl)- pyrrolidine (5 g) in 5N HCl (200 ml) was heated under reflux at 110°C for 16 hrs. The solution was evaporated under vacuum to dryness and the residue was crystallized from methanol/ether. Yield 3.6 g, 70.17%). NMR (D_2O) : 2.11-2.72 (m, 2H), 3.30-3.90 (m, 4H), 4.27 (s, 2H), 5.18-5.48 (m, 1H), 7.30 (s, 5H), 8.30 (s, 1H).

Example AA

3-(4-carboxy-1,2,3-triazol-1-yl)pyrrolidinehydrochloride

To a solution of N-benzyl-3-(4-carboxy-1,2,3-triazol-1-yl)pyrrolidine hydrochloride (1 g, 0.0033 mol) in methanol (50 ml) was added 10% Pd/C (100 mg) and conc. HCl (0.5 ml). The suspension was hydrogenated at r.t. and 50 psi pressure for 20 hrs. The Pd/c was removed by filtration and the solution was concentrated. The residue was recrystallised from methanol/ether to obtain white crystalline title compound. Yield 650 mg (93.25%) NMR (D_2O) : 2.51-3.56 (m, 2H), 3.62-3.75 (m, 2H), 3.92-4.00 (m, 2H), 5.52-5.67 (m, 1H), 8.67 (s, 1H).

Example BB

3(-5-carboxy-ethyl-1,2,3-triazol-1-yl)pyrrolidine hydrochloride

To a solution of N-benzyl-3(5-carboxy-ethyl-1,2,3-triazol-1-yl)pyrrolidine hydrochloride (2 g, 0.0061 mol) in methanol (100 ml) was added 10% Pd/c (200 mg) and conc. HCl (1 ml). The suspension was hydrogenated at r.t. and 50 psi pressure for 20 hrs. The Pd/c was removed by filtration and the solution was concentrated. The residue was crystallized from methanol/ether to obtain crystalline white compound. Yield 135 mg (93.29%) ^{1}H NMR (D_2O): 1.42 (t, 3H), 2.52-2.86 (m, 2H), 3.65-3.75 (m, 2H), 3.87-4.08 (m, 2H), 3.47 (q, 2H), 5.58-5.69 (m, 1H), 8.69 (s, 1H).

Example CC

N-benzyl-3(-4-phenyl-1,2,3-triazol-1-yl)pyrrolidine and N-benzyl-3(5-phenyl-1,2,3-triazol-1-yl)pyrrolidine

A solution of N-benzyl-3-azido pyrrolidine (3 g, 0.0148 mol) and phenyl-acetylene (3 g, 0.0292 mol) in benzene (30 ml) was heated under reflux for 48 hrs. The reaction mixture was concentrated to oil from which the title compounds were isolated by column chromatography using silica gel and a mixture of $CHCl_3$, hexane, MeOH (4:4:1) as eluant. N-benzyl-3(-5-phenyl-1,2,3-triazol-1-yl)pyrrolidine was obtained as oil. Yield 1 g (22.17%) ^{1}H NMR ($CDCl_3$) : 2.32-2.51 (m, 2H), 2.88-3.13 (m, 2H),

3.80 (s, 2H), 5.00 (p, 1H), 7.20-7.53 (m, 10H), 7.67 (s, 1H). N-benzyl-3-(4-phenyl-1,2,3-triazol-1-yl)-pyrrolidine, oil, yield 3.0 g ( ). ^{1}H NMR ($CDCl_3$) : 2.05-2.22 (m, 1H), 2.30-2.69 (m, 2H), 2.75-3.25 (m, 3H), 5.20-5.33 (m, 1H), 7.23-7.51 (m, 8H), 7.81-7.92 (m, 2H), 8.06 (s, 1H).

Example DD

3-(4-phenyl-1,2,3-triazol-1-yl)-pyrrolidinehydrochloride

A suspension of N-benzyl-3-(4-phenyl-1,2,3-triazol)pyrrolidine (2.0 g), concentrated HCL (0.5 ml) and 10% Pd/C (200 mg) in methanol was hydrogenated following the procedure given in example 53. Yield 1.32 g ( ). ^{1}H NMR (D_2O) : 2.35-2.72 (m, 2H), 3.57 (z, 2H), 3.84 (d, 2H), 5.35-5.45 (m, 1H), 7.35-7.65 (m, 5H), 8.23 (s, 1H).

Example EE

N-benzyl-3-(4-carboxy-hydrozido,1,2,3-triazol-1-yl)pyrrolidine

A suspension of N-benzyl-3-(4-carboxy-ethyl-1,2,3-triazol-1-yl)pyrrolidine (5.6 g, 0.0186 mol) and $NH_2NH_2.H_2O$ (2.36 g, 0.067 mol) in water (1.6 ml) was heated at 120 C for 10 hrs. The reaction mixture was then cooled to r.t. and stirred with 15 ml of ether. The separated solid was filtered and washed with water. The white solid thus obtained was dried in oven at 40 C. Yield 3.8 g (71.29%), m.p.=122.6°C. ^{1}H NMR : 1.96-2.14 (m, 1H), 2.36-3.15 (m, 5H), 3.7 (s, 2H), 4.05 (bs, 2H), 5.20-5.34 (m, 1H), 7.3 (s, 5H), 8.24 (s, 1H), 8.39 (s, 1H).

Example FF

N-benzyl-3-(4-carboxy-azido-1,2,3-triazol-1-yl)pyrrolidine

N-benzyl-3-(4-carboxy-hydrazide-1,2,3-triazol-1-yl)pyrrolidine (3.6 g, 0.0125 mol) was dissolved in hot water (40 ml) and then cooled to 0 C. To the cooled suspension $NaNO_2$ (950 mg, 0.0137 mol in 3 ml H_2O) was added dropwise and then glacial AcOH (7 ml) added to the

reaction mixture was stirred at 0 C for 15 min. Reaction mixture was then neutrallized by the addition of saturated $NaHCO_3$. The separated white solid was filtered and washed with water, dried in vacuum oven. Yield 3.73 g (100%), m.p. 160°C, ^1H NMR ($CDCl_3$) : 1.95-2.15 (m, 1H), 2.37-2.83 (m, 3H), 2.94-3.22 (m, 2H), 3.70 (d, 2H), 5.75-5.87 (m, 1H), 7.30 (s, 5H), 8.47 (s, 1H).

Example GG

N-benzyl-3(-4-t-butyl-carbonyl-amino-1,2,3-triazol-1-yl)pyrrolidine

A solution of N-benzyl-3(-4-carboxy-azido-1,2,3-triazol-1-yl)pyrrolidine (1 g, 2.91 mmol) in t-butanol (15 ml) was refluxed for 15 hrs. The reaction mixture was evaporated to dryness. Pure title compound was obtained as oil by purification on silica gel column using $CHCl_3$/MeOH as eluant. Yield 700 mg (60.86%). ^1H NMR ($CDCl_3$) : 1.52 (s, 9H), 2.41-2.65 (m, 2H), 2.77-3.11 (m, 4H), 3.70 (s, 2H), 3.56-3.73 (m, 1H), 7.30 (s, 5H), 7.94 (s, 1H).

Example HH

N-benzyl-3(-4-amino-1,2,3-triazol-1-yl)pyrrolidine dihydrochloride

A solution of N-benzyl-3(-4-t-butyl-carbamoyl-1,2,3-triazol-1-yl)pyrrolidine (100 mg 0.291 mmol) and conc. HCl (0.5 ml) in methanol (5 ml) was stirred at r.t. for 30 min. The solution was evaporated to dryness and the residue crystallized from methanol/ether to obtain title compound as a solid. Yield: 90 mg (98.9%), NMR (D_2O) : 2.52-3.0 (m, 2H), 3.55-4.70 (m, 4H), 4.60 (s, 2H), 5.50-5.76 (m, 1H), 7.60 (s, 1H), 8.03 (s, 1H)

Example II

3-(4-amino-1,2,3-triazol-1-yl)pyrrolidinedihydrochloride

To a solution of N-benzyl-(4-t-butyl-carbamoyl-1,2,3-triazol-1-yl)pyrrolidine-dihydrochloride (700 mg) in methanol 5% Pd/c (200 mg) was added. The suspension was hydrogenated at r.t. and 50 psi pressure over 30 hrs. The

Pd/c was removed by filtration and the solution was concentrated. The residue was crystallized from methanol/ether to white solid. Yield: 440 mg (95.8%). NMR (TFA) : 2.70-3.16 (m, 2H), 3.8-4.50 (m, 4H), 5.60-6.15 (m, 1H), 8.12 (s, 1H). The title compound was also obtained by hydrogenation of N-benzyl-(4-amino-1,2,3-triazol-1-yl)pyrrolidine hydrochloride in a yield of 92% following the procedure as given above.

Example JJ

N-Benzyl-3 (1,2,3,4-tetrazol-1-yl)pyrroline and N-Benzyl-3-1,2,3,4-tetrazol-2-yl)pyrrolidine

A suspension of N-benzyl-3-mesyloxypyrrolidine (2.2 g, 9.87 mmole) and sodium 1,2,3,4-tetrazolide (1.8 g, 19.6 mmole) in 50 ml of dimethylformamide was heated at 85-90°C overnight. The reaction mixture was worked up the same as described in Example I. The crude product was purified over silica gel using hexane, ether, and ethyl acetate as eluant to afford in order of elution 0.413 g of N-benzyl-3 (1,2,3,4-tetrazol-2-yl)pyrrolidine as an oil. ^{1}H NMR ($CDCl_3$) : 8.51 (s, 1H), 7.37-7.17 (m, 5H), 5.51-5.35 (m, 1H), 3.8-3.65 (q, 2H), 3.3-2.4 (m, 6H); and .26 g of N-benzyl-3-(1,2,3,4-tetrazol-1-yl)pyrrolidine as an oil. H NMR ($CDCl_3$: 8.88 (s, 1H), 7.4-7.2 (m, 5H), 5.35-5.2 (m, 1H), 3.83-3.6 (q, 2H), 3.2-2.3 (m, 5H, 2.15-2.00 (m, 1H).

Example KK

3-(1,2,3,4-tetrazol-2-yl)pyrrolidine hydrochloride

The N-benzyl-3-(1,2,3,4-tetrazol-2-yl)pyrrolidine (0.4 g) was hydrogenated under similar conditions as described for Example J for 21 hrs to yield 280 mg title product as hydrochloride salt after cyrstallization with methanol ether. ^{1}H NMR (D_2O) : 8.84 (s,1H), 6.05-5.86 (m, 1H), 4.18-3.87 (m, 2H), 3.8-3.6 (m, 2H), 2.94-2.55 (m, 2H).

Example LL

3-(1,2,3,4-tetrazol-1-yl)pyrrolidine hydrochloride

The N-benzyl-3-(1,2,3,4-tetrazol-1-yl)pyrrolidine (0.214

g) was hydrogenated under similar conditions as described for Example J for 21 hrs to yield 80 mg of title product as hydrochloride salt. ^{1}H NMR (D_2O) : 9.31 (s, 1H), 5.82-5.63 (m, 1H), 4.02-3.85 (m, 2H), 3.8-3.56 (m, 2H), 2.88-2.44 (m, 4H).

The structures of the intermediates and of compounds of the invention were established by the modes of synthesis and by extensive high field nuclear magnetic resonance spectral techniques.

The compounds of the invention display antibacterial activity when tested by the broth microdilution method as described in the NCCLS publications M7-A, M11-A and M17-P of the year 1985. For aerobic microorganisms, a cation supplemented Mueller Hinton Broth (BBL) was used whereas the Anaerobe Broth MIC (Difco) was used for anaerobic microorganisms. An agar Dilution method was employed for certain aerobic microorganisms using Mueller Hinton II Agar (BBL) and a Cathra multipoint inoculating device which delivered 10^4 cfu/spot of the inoculum on the agar surface. MICs were read after 16-18 hours and 48 hours of incubation in case of microbes growing aerobically and anaerobically respectively.

By use of the above method, the following minimum inhibitory concentration values (MICs in µg/ml) were obtained: Table 1, against microbes growing aerobically; Table 2, against microbes growing anaerobically; Table 3, against methicillin resistant Staphylococcus aureusand quinoline resistant-methicillin resistant Staphylococcus aureus.

TABLE 1

In vitro Antimicrobial Activity Against Aerobes
MIC (µg/ml)

Example No.	Staphylococcus aureus S-127
2	≤.06
4	≤.06
5	≤.03
6	≤.03
7	.008
12	.008
13	.008

14	≤.015
15	.015
16	.015
17	1
18	.5
19	.5
20	-
Sparfloxacin	.06
Ciprofloxacin	.25

TABLE 2

In Vitro Antimicrobial Activity Against Anaerobes
MIC (µg/ml)

Example No. / Microbes	11	12	14	SPAR	CIP
Bacteroides fagilis AN-2	1	1	> 64	2	16
Fusobacterium mortiferum AN-13	.06	.06	2	.50	16
Propionobacterium acne AN-17	≤.03	.06	.06	1	.50
Peptostreptococcus asaccharolyticus AN-16	.06	.06	.12	4	4
Streptococcus intermedius AN-19	.06	.12	.06	.50	1

SPAR = Sparfloxacin, CIP = Ciprofloxacin

TABLE 3

In Vitro Antimicrobial Activity Against Methicillin Resistant *S. aureus* (MRSAs) and Quinoline Resistant MRSAs (QRMRSAs)

Microbes / Example No.	MRSA (6 C.I.) MIC range (µg/ml)	QRMRSA (8 C.I.) MIC range (µg/ml)
11	.004 - .008	.50 - 2
12	.004 - .008	.50 - 2
14	.008 - .03	1 - 8
15	.008 - .015	1 - 16
Sparfloxacin	.03 - .12	4 - 16
Ciprofloxacin	.25 - .50	16 - >64
Tosufloxacin	.015 - .03	2 - 16

C.I. = Clinical Isolates

In another test procedure, the compounds of the present invention showed antibacterial activity when tested by the standard broth microdilution method as described in the NCCLS document M7-A2. Approved standard: Method for Dilution Antimicrobial Susceptability Tests for Bacteria that Grow Aerobically - Second Edition, 1990. The test organisms were obtained from ATCC and clinical laboratories. The 96-well microtitre plates containing 100 ml of serially diluted test compounds in Mueller Hinton Broth (MHB) (conc. range 64-0.03 ug/ml) were

inoculated with 100 ml of bacterial suspension in MHB so that an inoculum size of 5 x 10^5 cfu/ml was achieved. The plates were shaken gently and incubated at 35° C for 18 hr after which the minimum inhibitory concentrations (MIC, ug/ml) at which no visible microbial growth occurred were recorded.

The abbreviations for the test organisms used Table 4 below are as follows:

Ec. (S- 63): Escherichia coli
Ecl (S-130): Enterobacter cloacae
Pa. (S- 67): Pseudomonas aeruginosa
Kp. (S- 80): Klebsiella pneumoniae
Pr. (S-121): Providencia rettgeri
Sa. (S-127): Staphylococcus aureus

ANTIMICROBIAL ACTIVITY (MIC, UG/ML)

Microbroth Dilution (MHB) method; Inoculum, 5 x 10^5 cfu/ml; Incubation 35 C/18 hr

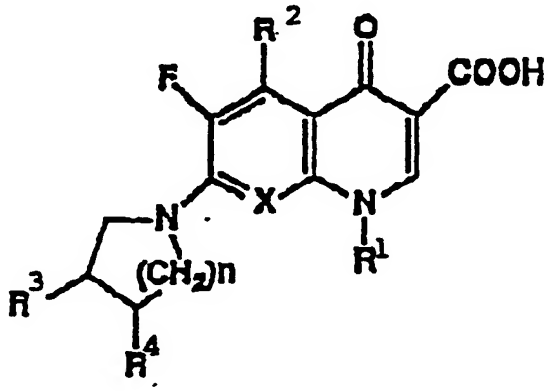
Example No.	Ec. S-63	Ecl. S-130	Pa S-67	Kp S-80	Pr S-121	Sa S-127	Sa. 127N
21	.06	.25	2	.25	.12	.015	.015
22	.25	1	4	.5	2	.125	.5
23	-	-	-	-	-	.03	-
24	.25	.25	4	.5	.25	≤.015	.12
25	.12	.25	4	.5	.5	≤.015	≤.015
26	.12	.25	4	.5	.5	≤.015	≤.015
27	.06	.25	2	.25	.25	≤.015	.03
28	.25	2	8	1	1	.03	.06
29	.25	1	4	.5	2	.125	.25
30	.12					≤.015	
31	.06	.25	2	.25	.5	≤.03	.03
32	.12	.25	4	.5	.25	.03	.06
34	.12	.5	2	.25	.5	≤.015	≤.015
35	.12	.5	4	.25	.12	≤.03	≤.03
36	.12	1	8	.1	2	≤.015	≤.015
37	.5	.5	8	.5	.5	.5	1
38	.25	.5	4	.25	.25	≤.015	.03
40	.5	2	8	1	1	.06	.25
41	.25	1	8	1	1	.12	.5

42	.25	1	8	1	1	.03	.12
43	1	1	8	1	.5	1	.5
44	.12	-	-	-	-	.03	-
45	.5	1	4	1	1	.25	1
46	16	32	>32	32	32	8	8
47	.5	.25	8	1	1	25	-
48	.25	-	-	-	-	-	1
49	.25	1	32	1	.015	.015	.015
50	.25	16	>32	.5	.015	.015	.015
51	1	4	16	4	.015	.015	.015
52	.5	.50	8	.5	.12	.25	.25
53	1	2	16	1	.06	.25	.25
54	.06	-	2	.12	.12	≤.03	≤.03
55	.06	-	2	.25	.12	.06	-
CPLX	≤.008	.03	.25	.015	.015	.25	8
NFLX	.06	.12	1	.12	1	1	16
NFLX-Ch	.06	.25	1	.25	.12	2	16

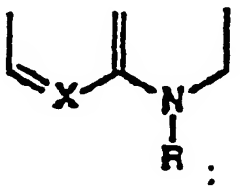
While the invention has been particularly shown and described in reference to preferred embodiments, it will be understood by those skilled in the art that changes in form and details may be made without departing from the spirit and scope of the invention. For example the compounds disclosed and described could be used in compositions to disinfect surfaces in environments where food is prepared.

WHAT IS CLAIMED

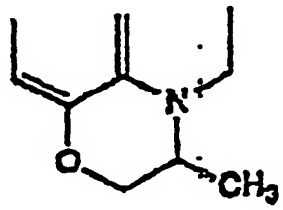
1. A 7-substituted-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid compound of the formula:



wherein R^1 is a C_3-C_6 cycloalkyl group or a phenyl group which may be substituted by one or two halogen atoms;
R^2 is hydrogen, a halogen atom, a C_1-C_4 alkyl group, a hydroxy group or an amino group;
R^3 is hydrogen, hydroxy or amino;
R^7 is a 1,2,3-triazol-1-yl group, a 1,2,4-triazol-1-yl group, a 1,2,3,4-tetrazol-1-yl or a 1,2,3,4-tetrazol-2-yl group, each of which may have 1 to 2 substituents selected from the group consisting of C_1-C_4 alkyl, COOH, CH_2NH_2, amino and phenyl groups; and X is N, CH, C-F or C-OCH_3;
n is 0, 1 or 2; or



may be



;

or a pharmaceutically acceptable salt thereof.

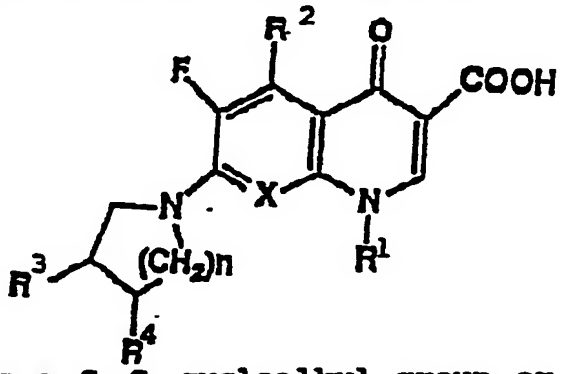
2. A compound according to claim 1, wherein R_1 phenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,4-dimethoxyphenyl or 4-aminophenyl.

3. A compound according to claim 1, wherein R_1 is optionally substituted by chloro, fluoro, bromo, methoxy or amino.

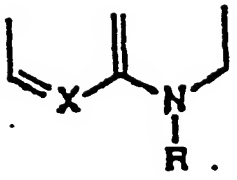
4. A compound according to claim 1, wherein n=1 and the compound has an asymmetric carbon atom on the pyrrolidine ring, and the compound is the R isomer, the S isomer or mixtures thereof.

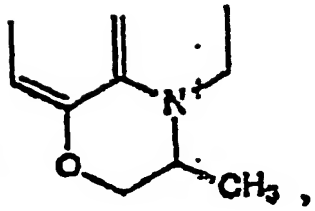
5. A compound according to claim 1, wherein n=1 and the compound has two asymmetric carbon atoms on the pyrrolidine ring, and the compound is a stereoisomer structures of the cis or trans configuration, or mixtures thereof.

6. A process for preparing a 7-substituted-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid compound of the formula:

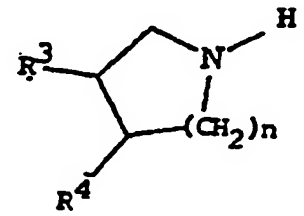


wherein R^1 is a C_3-C_6 cycloalkyl group or a phenyl group which may be substituted by one or two halogen atoms;
R^2 is hydrogen, a halogen atom, a C_1-C_4 alkyl group, a hydroxy group or an amino group;
R^3 is hydrogen, hydroxy or amino;
R^7 is a 1,2,3-triazol-1-yl group, a 1,2,4-triazol-1-yl group, a 1,2,3,4-tetrazol-1-yl or a 1,2,3,4-tetrazol-1-yl group, each of which may have 1 to 2 substituents selected from the group consisting of C_1-C_4 alkyl, COOH, CH_2NH_2, amino and phenyl groups; and
X is N, CH, C-F or C-OCH_3;
n is 0, 1 or 2; or

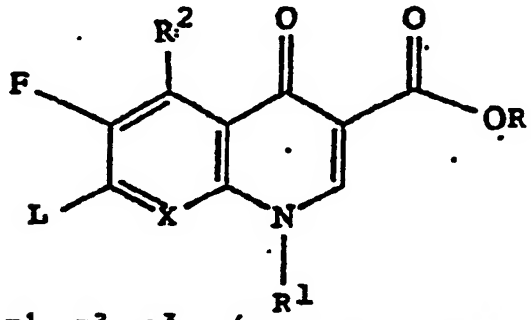


may be  ;

or a pharmaceutically acceptable salt thereof, said process comprising reacting a compound of the formula



with a compound of the formula



wherein R, R^1, R^2, R^3, R^4, n and X are as defined above;

L is a leaving group selected from chlorine fluorine or SO_2R_7, wherein R_7 is C_1-C_4 alkyl group substituted or unsubstituted phenyl group.

7. A pharmaceutical composition suitable for treating bacterial infections comprising an antibacterial amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

8. A method for treating a bacterial infection in humans which comprises administering to a human having a

bacterial infection an antibacterially effective amount of a compound of claim 1.

9. A method for disinfecting a surface to be disinfected which, comprises: treating the surface with a composition containing an antibacterial effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 91/00435

I CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 401/14 C 07 D 471/04 C 07 D 498/06
C 07 D 521/00 A 61 K 31/47 //(C 07 D 498/06 C 07 D 265:00
C 07 D 221:00)(C 07 D 471/04, 221:00, 221:00) (C 07 D 401/14, ./.

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 401/00 C 07 D 471/00 C 07 D 498/00 C 07 D 521/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0388298 (LABORATORIOS DEL Dr ESTEVE S.A.) 19 September 1990, see claims 1-6; example 41 ---	1-7
A	EP,A,0387802 (BRISTOL-MYERS SQUIBB COMPANY) 19 September 1990, see claims 1,12-14; table 3 ---	1-7
A	EP,A,0350733 (BAYER AG) 17 January 1990, see claims 1,7; table 1 ---	1,7
A	EP,A,0203488 (BAYER AG) 3 December 1986, see claims 1,6,11 ---	1,7
A	EP,A,0172651 (WARNER LAMBERT COMPANY) 26 February 1986, see the whole document (cited in the application) --- -/-	1-7

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27-01-1992	12. 03. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Maria Pels Maria Pels

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 91/00435 -2-

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 D 257:00, 215:00, 207:00)(C 07 D 401/14, 249:00, 215:00, 207:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	Chemical Abstracts, volume 104, 1986, (Columbus, Ohio, US) see page 712, abstract 109495g, & JP, A, 60166681 (FUJISAWA PHARMACEUTICAL CO. LTD) 29 August 1985, see abstract compound with RN=100501-49-3	1,6,7

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1 ☒ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Remark: "Although claim 8 is directed to a method of treatment of (diagnostic method practised on) the human body the search has been carried out and based on the alleged effects of the compound/composition."

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4 ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. CA 9100435 SA 53771

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/03/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0388298	19-09-90	FR-A- 2644455	21-09-90
		FR-A- 2649106	04-01-91
		FR-A- 2654728	24-05-91
		AU-A- 5137590	20-09-90
		CA-A- 2012223	16-09-90
		JP-A- 2279683	15-11-90
EP-A- 0387802	19-09-90	AU-A- 5123690	13-09-90
		CA-A- 2011939	13-09-90
		CN-A- 1045972	10-10-90
		JP-A- 2282384	19-11-90
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		JP-A- 2069474	08-03-90
		US-A- 4990517	05-02-91
		US-A- 5059597	22-10-91
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		JP-A- 61277669	08-12-86
EP-A- 0172651	26-02-86	AU-B- 602585	18-10-90
		AU-A- 1731288	25-08-88
		AU-B- 613372	01-08-91
		AU-A- 1731388	15-09-88
		AU-B- 576252	18-08-88
		AU-A- 4458185	23-01-86
		JP-A- 61043186	01-03-86
		US-A- 4822801	18-04-89

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82